An Oral History Of Neuropsychopharmacology

The First Fifty Years

Peer Interviews

SERIES EDITED BY: Thomas A. Ban

Volume Four:
PSYCHOPHARMACOLOGY

EDITED BY: Jerome Levine

American College of Neuropsychopharmacology

AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

THE FIRST FIFTY YEARS

Peer Interviews

Volume Four: Psychopharmacology

Copyright © 2011 ACNP

Thomas A. Ban (series editor)
AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

Jerome Levine (volume editor)
VOLUME 4: PSYCHOPHARMACOLOGY

All rights reserved. No part of this book may be used or reproduced in any manner without written permission from the American College of Neuropsychopharmacology (ACNP).

Library of Congress Cataloging-in-Publication Data
Thomas A. Ban, Jerome Levine (eds):
An Oral History of Neuropsychopharmacology: The First Fifty Years, Peer Interviews
Includes bibliographical references and index
ISBN: 1461161673
ISBN-13: 9781461161677

1. Psychopharmacology 2. Clinical methodology
3. Early Clinical Drug Evaluation Unit Network
4. Biometric Laboratory Information Processing System

Publisher: ACNP
ACNP Executive Office
5034A Thoroughbred Lane
Brentwood, Tennessee 37027
U.S.A.
Email: acnp@acnp.org
Website: www.acnp.org

Cover design by Jessie Blackwell; JBlackwell Design www.jblackwelldesign.com

AMERICAN COLLEGE OF NEUROPSYCHOPHARMACOLOGY

AN ORAL HISTORY OF NEUROPSYCHOPHARMACOLOGY

THE FIRST FIFTY YEARS

Peer Interviews

Edited by
Thomas A. Ban

Co-editors

Volume 1: Starting Up - Edward Shorter
Volume 2: Neurophysiology - Max Fink
Volume 3: Neuropharmacology - Fridolin Sulser
Volume 4: Psychopharmacology - Jerome Levine
Volume 5: Neuropsychopharmacology - Samuel Gershon
Volume 6: Addiction - Herbert D. Kleber
Volume 7: Special Areas - Barry Blackwell
Volume 8: Diverse Topics - Carl Salzman
Volume 9: Update - Barry Blackwell
Volume 10: History of the ACNP - Martin M. Katz

VOLUME 4

PSYCHOPHARMACOLOGY

ACNP
2011

VOLUME 4

Jerome Levine

PSYCHOPHARMACOLOGY

Preface
Thomas A. Ban

Dedicated to the Memory of Arnold J. Friedhoff, ACNP President, 1978

PREFACE
Thomas A. Ban

The term, psychopharmacology was introduced in 1920 by David Macht, an American pharmacologist for describing the effects of drugs on psychometric performance tests.[1] The scope of psychopharmacology was gradually extended and by the 1960s it embraced all research dedicated to study the effects of centrally acting drugs.[2]

In this series, the broad, all embracing concept of "psychopharmacology," is deconstructed into its component disciplines: Volume One, Starting Up, deals with measurable changes caused by drugs on behavioral parameters ("behavioral pharmacology"); Volume Two, Neurophysiology, deals with the impact of drugs on cerebral metabolism and electrical activity; Volume Three, Neuropharmacology, on molecular and sub-molecular brain structures; and Volume Four, Psychopharmacology, on mental faculties and psychopathology. Thus, in this volume, interviewees reflect on their contributions to psychopharmacological research.

The story begins in the 1950s with the serendipitous discovery of effective pharmacological treatments for schizophrenia (chlorpromazine and reserpine), depression (iproniazid and imipramine), mania (lithium), and anxiety (meprobamate.)[3] The new drugs were received incredulously by the psychiatric establishment.[4] Yet by the end of the 20th century drug therapy was the primary form of treatment in the majority of psychiatric disorders.

Central to psychopharmacological research is the identification of pharmacologically homogeneous populations within the pharmacologically heterogeneous psychiatric diagnoses. The need for a pharmacological re-evaluation of psychiatric nosology[5] led to the development of the AMP documentation system in German speaking countries. To overcome the difficulty of demonstrating therapeutic efficacy in pharmacologically heterogeneous diagnostic population, the BLIPS was developed in the United States. Both systems were introduced in the 1960s and are defined below.

The AMP System

Activities which led to the introduction of the AMP System began in the late 1950s by two independent teams of university based psychiatrists, one

in the Federal Republic of Germany (FRG) and the other in Switzerland, collaborating in clinical studies with psychotropic drugs.*

In the early 1960s, members of the two groups, together with Peter Berner from the Department of Psychiatry, University of Vienna (Austria,) and Paul Schmidlin from Geigy, a Swiss pharmaceutical company, embarked on the development of a common documentation system for studying and characterizing the clinical effects of the new drugs. The working relationship was formalized in 1965 by the founding of the Arbeitsgemeinschaft für Methodik und Documentation in der Psychiatry (Working Group for the Methodology and Documentation in Psychiatry) with a secretariat at the Psychiatric Clinic of the Free University in West Berlin. The documentation system, completed in 1967, was referred to as the AMP System, using the acronym of the Working Group.[6] In the 1970s, the acronym was changed to AMDP.[7]

The AMDP System consists of five integrated forms for recording: (1) Demographic Data, (2) Life Events, (3) Psychiatric History, (4) Psychopathological Symptoms (PSF), and (5) Somatic Signs (SSF). Two of the five forms, the PSF and the SSF, are suitable for the assessment of change in the clinical state of patients. The PSF includes 100 items, organized into 13 categories;** the SSF consists of a catalogue of 41 physical symptoms (signs), listed under seven headings.[8]*** Programs for computer processing of the AMP (AMDP) data were developed in the 1960s and 1970s at several centers, including Berlin, Erlangen, Munich and Zurich.[9]

Since its first edition, in 1971,[10] the AMP (AMDP) Manual has been revised several times. It's most recent, eighth edition, was published in 2007.[11]

The Manual was translated into several languages**** because it seemed a more suitable instrument for the delineation of the therapeutic profile of psychotropic drugs than the conventional rating scales used in clinical trials.[12]

The initial English translation was completed from the second edition of the Manual [13] by Jüri Saarma, in collaboration with Thomas Ban and Heinz Lehmann (see Lehmann, Volume 1), in 1974.[14] Saarma, chairman of

* The psychiatrists in the FDR included: D. Bente (Erlangen,) M.P. Engelmeier (Essen,) K. Heinrich (Düsseldorf,) H. Helmchen and H. Hippius (Berlin,) and N. Schmitt (Saarbrücken.) The psychiatrists in Switzerland included: J. Angst (Zurich,) F. Cornu (Bern,) P. Dick (Geneva,) H. Heimann (Lausanne,) and O. Pöldinger (Basel.)

** The thirteen categories of the PFS: (1) intellectual deficit, (2) disorders of consciousness, (3) disturbance of orientation, (4) disturbance of attention and memory, (5) formal disorders of thought, (6) phobias and compulsions, (7) delusions, (8) disorders of perception, (9) disorders of ego, (10) disturbances of affect, (11) disorders of drive and psycho-motility, (12) circadian disturbances, and (13) other disturbances, including social withdrawal, excessive social contact, aggressiveness, suicidal tendencies, self-mutilation, lack of feeling ill, lack of insight, uncooperativeness and lack of self-care.

*** The seven headings of the SSF catalogue: (1) disturbance of sleep and vigilance, (2) appetite disturbances, (3) gastrointestinal disturbance, (4) cardiac-respiratory disturbances, (5) other autonomic disturbances, e.g., blurred vision, (6) other somatic disturbances, e.g., headache, and (7) neurological disturbances.

**** The manual was translated into Croatian, Dutch, English, Estonian, French, Greek, Italian, Japanese, Portuguese, Russian, and Spanish.

the Department of Psychiatry at the University of Tartu (Dorpat), where Emil Kraepelin began his career, was at the time Visiting Professor with the WHO Training Program in Biological Psychiatry in Montreal, Canada .(See Ban in this Volume and Volume 9.)

In 1977, the third German edition of the system, now called AMDP-III, was published.[15] The changes in AMDP-III were significant enough to warrant a new English translation. This was prepared by Guy and Ban* and published in 1982.[16] The advent of AMDP-III has created a similar situation for other translations[17, 18] To coordinate activities among the groups involved with AMDP outside of German speaking countries, an International AMDP Secretariat was established at The University of Liege, Belgium, under the leadership of Daniel Bobon.[19]

To render studies conducted with the AMDP accessible for data processing and analyses by BLIPS, William Guy prepared a series of input matrices for the five forms of the system with the employment of universal op-scan data sheets.[20]

The BLIPS

The development which led to the Biometric Laboratory Information Processing System, (BLIPS) began in 1956 with the establishment of the Psychopharmacology Service Center (PSC,) by NIMH, and the appointment of Jonathan O. Cole as its director. (See Cole in this Volume, and also in Volumes 9 & 10.) The Center was mandated to facilitate the clinical development and adoption into clinical practice of the rapidly growing number of new drugs with psychotropic potential. To accomplish this task, Cole launched the NIMH Collaborative Studies with Phenothiazines in the Treatment of Schizophrenia, embarked on the development of the Early Clinical Drug Evaluation Unit (ECDEU) network (program), and established a Biometric Laboratory at George Washington University for developing a data collection, processing and reporting system with a data bank for clinical trials. The system, developed by the staff of the Laboratory, in collaboration with the ECDEU investigators, was to be referred as BLIPS.

By January 1962, the ECDEU network included 15 centers investigating a total of 48 new drugs; by the mid-1960s, the BLIPS, was ready to analyze clinical trials conducted by ECDEU investigators. The computer-generated “output package” consisted of a standardized report that included a brief description of the clinical study, the findings of statistical analyses

* The manual was prepared by Guy and Ban in collaboration with D. Bobon, J. Hoenig, R. Jamieson, Y. Lapierre, A.Leeds, H. Lehmann, J. Libiger and J.Saarma, and consultation with J. Angst, P. Berner, P. Grof, M. Hamilton, H. Helmchen, M. Hollender, E. Koranyi and N. Sartorius.

and tabulations of recorded data on the various assessment instruments employed.[21]

In 1968, the Laboratory offered to analyze any clinical study, and not just studies done within the network, in which the ECDEU assessment battery was employed.

The first ECDEU Assessment Manual was prepared by William Guy and Roland Bonato in 1970.[22] A revised, enlarged manual, with the inclusion of 43 scales was published in 1976 by Guy.[23] Notably, the revised Manual serves as a guide for selecting the appropriate data collection forms for the three successive phases of clinical investigations: the Planning Phase, the Data Collection Phase and the Analytic Phase.*

Following the publication of the revised manual there was an expansion in the use of the BLIPS from a limited number of ECDEU investigators to a rapidly growing number in Canada and the United States. The ECDEU network was dismantled, and replaced by the New Clinical Drug Evaluation Units (NCDEU) network, which included clinical investigators using the BLIPS regardless of NIMH support. Having fulfilled its purpose by developing a data processing system for clinical investigations with psychotropic drugs, in the late 1970s the Biometric Laboratory at George Washington University was closed. Since interest in the BLIPS continued, in the early 1980s a Center for Clinical Psychopharmacology Documentation was set up by Jerome Levine, Cole's successor,** with NIMH support at the Psychiatric Clinic II of the University of Pisa in Italy for clinical investigators in Europe.

Introduction of the BLIPS has had a major impact on the development of a clinical methodology. During the 1970s testimonials about clinical effects were replaced by findings in properly designed clinical experiments and by the early 1980s the double- blind, placebo-controlled clinical trial with random assignment of patients to parallel treatment groups (RCT,) had become standard for efficacy studies with psychotropic drugs. As multi-center clinical investigations were replacing single center clinical trials, in the 1980s power statistics entered the design in order to prevent a type-II beta error; the over-

* Obligatory forms to be used in all clinical investigations. Analytic Planning Phase: Research Plan Report and the ECDEU Assessment Instrument Order Form. Data Collection Phase: Dosage Record and Treatment Emergent Symptom Scale, the Clinical Global Impressions, and the Patient Termination Record. Analytic Phase: Research Completion Report and the Data Shipment Form. Scales recommended to be used in the assessment of change. Studies with neuroleptics: Brief Psychiatric Rating Scale (BPRS) and Nurses Observation Scale for Inpatient Evaluation (NOSIE) Studies with antidepressants: Hamilton Psychiatric Rating Scale for Depression (HAMD), Depression State Inventory (DSI) and Self-rating Scale for Depression (SRSD). Studies with anxiolytics: Hamilton Anxiety Scale (HAMA), Anxiety Status Inventory (ASI), Self-rating Anxiety Scale (SRAS) and Self Report System Inventory (SRSI).

** Jonathan Cole left NIMH in 1967. He was succeeded by Jerome Levine. In 1968 the PSC was converted into the Psychopharmacology Branch of NIMH with Levine as its first chief.

looking of a statistically significant difference between placebo and an investigational drug because of insufficient sample size.[24]

Simultaneously with the changes in methodology, descriptive statistics were complemented with non-parametric statistical techniques (chi square test, Mood's median test, the Mann-Whitney U-test and the Wilcoxon matched-pairs signed rank test) in the analyses of data. As the sample size of studies grew, non-parametric statistical techniques were replaced by parametric statistical techniques (Student's t-test, analyses of variance and covariance,) assuming that in larger samples rating scores have a Gaussian normal distribution.[25]

Diagnostic End Points

The clinical end-points of efficacy studies are psychiatric diagnoses. The first consensus based diagnostic classification with a glossary of definitions was DSM-I of the American Psychiatric Association.[26] A variant of WHO's, ICD-6,[27] DSM-I, was introduced in 1952, just about the time chlorpromazine was launched for clinical use in France. Both classifications were replaced by the end of the 1960s: ICD-6, first by ICD-7, in 1955,[28] then by ICD-8, in 1965,[29] and DSM-I by DSM-II in 1968.[30]

There were conflicts between diagnoses in the consensus-based classifications and the classification of psychotropic drugs. West and Dally found iproniazid, a monoamine oxidase inhibitor (MAOI,) classified as an antidepressant, effective in a group of patients who showed opposite features, such as hypersomnia and hyperphagia, to those encountered in patients who would qualify for a depressive diagnosis in the ICD-7 or DSM-I[31]; Sargant and Dally reported on the effectiveness of MAOIs in "anxiety states,"[32] and several clinicians noted that some MAOIs, e.g., phenelzine, could control phobic-anxiety-depersonalization, a syndrome with spontaneously recurring anxiety (panic) attacks, described by Martin Roth in 1959.[33,34]

In order to facilitate a classification of psychiatric disorders which corresponds more closely than consensus-based diagnoses with the therapeutic profile of psychotropic drugs, the first multi-axial classifications were proposed by Wing and his associates in the UK,[35] Ottoson and Perris in Sweden, [36] Helmchen in Germany,[37,38] and Strauss in the United States.[39] The development of multi-axial classifications culminated in 1980 in the publication of DSM-III.[40]

DSM-III was the first consensus-based classification with a multi-axial evaluation and operationalized diagnostic criteria. Its development was linked to research focused on the verification of psychiatric diagnoses by "external validators," in the Department of Psychiatry of Washington

University in St.Louis, Missouri,[41] and, on the measurement of concordance in diagnosis (reliability) among clinicians by kappa statistics developed in the Biometric Research Department of the New York State Psychiatric Institute.[42] The diagnostic formulations of DSM-III combine both traditions of medicine, the tradition of Galen (131-201 AD) focused on disease, and the tradition of Hippocrates (460-370 BC) focused on the patient.[43] Thus, they contain categorical judgments regarding the disease, recorded on Axes I (clinical psychiatric syndromes) and Axis III (non-psychiatric medical illness), and dimensional ratings regarding the patient, recorded on Axis IV (severity of psychosocial stressor) and Axis V (level of adaptive functioning),[44] Personality disorders were separated from the clinical syndromes on Axis II. In spite of severe criticisms, DSM-III, and its successors, the DSM-III-R, published in 1987[45] and the DSM-IV, published in 1994,[46] have become an unprecedented success. The operationalized criteria for diagnostic decisions provided reliable clinical end-points for single-center and multi-center clinical investigations with psychotropic drugs.[47]

Interviewees and Interviewers

The preceding information provides orientation points in the development of psychopharmacology for placing in perspective the contributions of the interviewees.

From the thirty interviewees of Volume Four, twenty-three are MDs (Autry, Ban, Blackwell, Bowden, Cole, Gallant, Gardos, Goldstein, Kane, Klein D, Kocsis, Lecrubier, Levine, Lieberman, Paykel, Quitkin, Rickels, Schatzberg, Simpson, Uhlenhuth, Vinar, Wheatley and Winokur), and seven PhDs (Hogarty, Katz, Klett, McNair, Overall, Raskin and Schooler) All, but 1 of the MDs, David Wheatley, a general practitioner, are psychiatrists; and all but 1 of the PhDs, Gerard Hogarty, a social worker, are psychologists. All, but two of the interviewees, Lecrubier and Wheatley, are ACNP members; one of the interviewees, Autry, was, at the time of the interview, an administrative member. Four of the interviewees, Cole, Klett, Rickels and Uhlenhuth, are founders, and five, Cole, Klein D, Schatzberg, Simpson and Uhlenhuth, are past presidents.

All interviews were done in a period from 1994 to 2007, and with the exception of two interviews, Autry's and Klett's, they were done at annual meetings. Autry and Klett were interviewed in Washington, DC, between meetings.

The thirty interviews were done by ten interviewers with seven interviewers, Braslow, Endicott, Gershon, Healy, Kapur, Levine and Robinson, conducting one interview, and from the other three interviewers Tone conducting four, Ban nine, and Hollister ten.

By the time the editing of Volume Four was completed, five of the interviewees Cole, Hogarty, Lecrubier, Quitkin and Wheatley, and one of the interviewers, Hollister, had passed away.

Contributions of Interviewees

In the following section some of the contributions made by interviewees to the development of psychopharmacology are reviewed.

Two interviewees, Cole and Levine, were instrumental in developing **BLIPS** and implementing the clinical methodology that was to be used in efficacy studies with psychotropic drugs. *Jonathan O. Cole,* the founding director of PSC, lead the team that designed and organized the NIMH Collaborative Studies in which the effectiveness of the phenothiazine neuroleptics in the treatment of acute and chronic schizophrenia was conclusively demonstrated.[48,49,50] Cole was also first, in collaboration with Gerald (Jerry) Klerman, to demonstrate the efficacy of imipramine and related antidepressants in depressive disorders.[51]

Jerome Levine, the successor of Jonathan Cole as director of PSC, developed in collaboration with Nina Schooler (See Schooler in this Volume), the Abnormal Involuntary Movement Scale (AIMS) for rating the severity of tardive dyskinesia, and an instrument for recording side effects in clinical trials with psychotropic drugs, (SAFTEE).[52] Levine was a member of the team which demonstrated that LSD offers no benefit in chronic alcoholism,[53,54] a treatment advocated by Hoffer and Osmond in the 1960s.[55] (See Levine also in Volume 9.)

Numerous **NIMH** programs from the late 1950s to the end of the 1980s addressed issues relevant to the clinical use of psychotropic drugs. *Joseph H. Autry,* helped set up the collaborative research program in the treatment of depression in the early 1980s which indicated that only in "severe depression" was pharmacotherapy the primary choice of treatment.[56]

Findings in clinical investigations depend on the assessment instruments employed; five of the interviewees, McNair, Klett, Overall, Raskin and Vinar, were involved in the development of **rating scales** for the assessment of change in the course of treatment. *John E. Overall* with Donald Gorham developed the Brief Psychiatric Rating Scale (BPRS,) from Maurice Lorr's Multidimensional Scale for Rating Psychiatric Patients, (MSRPP).[57] The BPRS, introduced in 1962, was to become one of the most extensively used rating scales in clinical studies with psychotropic drugs.[58] Overall was first to apply "least squares analysis" for natural data with psychotropic drugs.[59] He also spearheaded the application of other statistical techniques in clinical research by publishing, with Klett in 1972, Applied Multivariate Analysis.[60]

James C. Klett, in collaboration with Gilbert Honigfeld, developed the Nurses Observation Scale for Inpatient Evaluation (NOSIE.) The NOSIE, introduced in 1965, was to become one of the standard assessment instruments in clinical trials with hospitalized psychiatric patients.[61] Klett was a member of the US Veterans Administration (VA) team which demonstrated the efficacy of phenothiazines in the treatment of schizophrenia in 1960.[62] He was also member of Lorr's team which developed the Inpatients Multi-dimensional Rating Scale (IMPS) from the MSRPP.[63]

Douglas McNair was also a member of Lorr's team converting the MSRPP into the IMPS.[64] In collaboration with Lorr and Droppleman, McNair introduced in 1971, the Profile of Mood States (POMS) that was to be used for the assessment of change in outpatient clinical trials.[65]

Allen Raskin, an associate of Jerome Levine at PRB in setting up NIMH's nine hospital antidepressant study,[66] developed, in the late 1960s, The Raskin Depression Rating Scale (RDRS).[67] With the employment of "reverse factor analysis," Raskin separated four distinct groups within the depressive population: "agitated," "neurotic," "endogenous" and "poor pre-morbid personality" depressions.[68]

Oldrich Vinar developed, in the early 1960s, scales for measuring changes in psychotic and depressive symptomatology in clinical studies, (FKP and FKD)[69,70] Vinar introduced the "continuous controlled clinical trial"[71] on his research unit in Czechoslovakia. He was instrumental in the development of several psychotropic drugs for the Czechoslovakian pharmaceutical industry, e.g., dosulepine, a chlorinated amitriptyline, dichlorpromazine, a minor tranquilizer, and isofloxythepine, a clozapine-like drug.[72]

Not all changes in rating scale scores could be attributed to the pharmacological action of psychotropic drugs; three of the interviewees, Rickels, Hogarty, and Schooler, were involved in research to determine the contribution of **other factors**. *Karl Rickels* led clinical research in the 1960s in studying the effect of non-specific factors on drug treatment.[73] He was also first in the United States, to organize a network of practitioners to collaborate in clinical investigations with these drugs.[74] Rickels contributed to the clinical development of some of the early anxiolyitc drugs, e.g., meprobamate, chlordiazepoxide and diazepam;[75] he also contributed to delineating the differential effect of antidepressants and anxiolytics in the first phase of treatment of generalized anxiety disorder.[76]

Gerard E. Hogarty, a member of Jonathan Cole's team in the NIMH Collaborative Studies in schizophrenia, explored systematically the interaction between social and pharmacological treatments in schizophrenia including personal therapy, major role therapy and cognitive enhancement training.[77,78] He was the first to show that social therapies alone, without

neuroleptics, might have a negative effect, whereas social therapies combined with neuroleptics could help patients in social adjustment.[79]

Nina R. Schooler, a member of the Cole/Levine group was involved with Hogarty's team studying the interaction between drugs and social therapies in the treatment of schizophrenia. In collaboration with Hogarty and Weissman, she developed SAS II, a Social Adjustmment Scale, (SAS 11), introduced in 1979.[80] Schooler participated in research on the clinical development of several "atypical antipsychotics," including aripiprazole, clozapine, risperidone, sertindole, and ziprasidone.[81,82]

Four of the interviewees, Katz, Paykel, Blackwell and Lecrubier were involved in the development of **assessment instruments**, other than the rating scales used in the assessment of change in clinical trials. *Martin M Katz*, one of the first members of Cole's team at the PSC, introduced the Katz Adjustment Scales in 1963 for measuring adjustment of social behavior in the community of patients discharged from hospital after successful pharmacological treatment.[83] He also developed a "video methodology" for research in psychopathology and psychopharmacology in the 1970s.[84,85] In an NIMH sponsored multi-center clinical investigation in depression, Katz and his associates demonstrated clinical changes within a week of commencement of treatment with SSRIs and TCAs[86] and challenged the theory about delayed onset of anti-depressant effects (See Sulser and Frazer, Volume 3).[87] The changes with paroxetine within the first week were in anxiety and hostility whereas the changes with desipramine were in retardation and depression.[88] (See Katz also in Volumes 9 & 10.)

Eugene S. Paykel, developed a "life events" scale in the late 1960s and was the first to verify the commonly held view that recent life events might play a role in the pathogenesis of some depression.[89] In the early 1970s, with the employment of cluster analysis, Paykel divided depressed patients into four groups: psychotic, anxious, hostile and depressives with personality disorder[90]. Paykel also corroborated evidence for the differential effect of the tricyclic antidepressant, amitriptyline, and the MAOI, phenelzine in the treatment of neurotic depression,[91] and for the efficacy of continuation and maintenance treatment with antidepressants in unipolar depression.[92]

The first validated screening instrument, for the identification of psychiatric disorders in primary care setting, the General Health Questionnaire (GHQ,) was developed by David Goldberg in collaboration with *Barry Blackwell.* With the employment of the GHQ, they found psychiatric morbidity in 1 out of every 5 patients seen by general practitioners.[93] Blackwell was one of the first to report on hypertensive crisis involving tranylcypromine in patients consuming cheese,[94] His discovery of cheese and the role of tyramine and other variables

in patients treated with MAOIs[95] has profoundly affected the pharmacological treatment of depression.[96]

Yves Lecrubier, in collaboration with David Sheehan, developed a brief, about 15 minute, structured interview, (MINI), which yields a DSM-IV and an ICD-10 diagnosis.[97] Lecrubier also developed an instrument for measuring "retardation," that he considered the cardinal symptom of depressive illness.[98] In his research in schizophrenia, Lecrubier substantiated the notion that low dose neuroleptics affect "deficit," whereas high dose neuopletics affect "productive" symptoms.[99,100]

Psychotropic drug development has been the driving force in psychopharmacological research; four of the interviewees; Ban, Gallant, Goldstein and Simpson, were involved, as **ECDEU investigators**, in clinical studies that led to the registration of several of the first generation psychotropic drugs *Thomas A. Ban* contributed to the clinical characterization of several phenothiazines,[101,102,103] butyrophenones,[104] thioxanthenes,[105,106,107] diphenylputylpepridines,[108,109] tricyclic[110,111,112] and other antidepressants.[113,114] He was first to detect the antidepressant effect of trazodone in the 1970s[115] and to demonstrate the antidepressant effect of reboxetine in the 1990s[116] He was also first in 1964 to report dose-dependent cardiac conduction changes with thioridazine.[117] To translate pharmacological findings into clinical effects, Ban developed in the 1960s a conditioning test procedure.[118] He also developed two instruments, DCR Budapest-Nashville (in collaboration with Bertalan Pethö),[119] and CODE-DD,[120] for the identification of pharmacologically more homgeneous diagnostic populations than in consensus-based classifications. Ban's findings indicate an inverse relationship between the therapeutic and adverse effects of psychotropic drugs, e.g., tardive dyskinesia with neuroleptics, toxic psychosis with lithium.[121]

Donald M. Gallant contributed to the clinical characteriztion of several psychotropic drugs, including triperidol,[122,123] thiothixene,[124] cinanserin,[125] penfluridol,[126] among others. He also extended clinical investigations with some of the new drugs, e.g., doxepin, to chronic alcoholism.[127] Gallant, and his team provided further substantiation of cardiac conduction changes with thioridazine, and were first to report on similar changes with mesoridazine.[128] As early as the 1970s, Gallant addressed ethical issues related to psychopharmacology research.[129]

Burton J. Goldstein contibuted to the clinical characterization of several psychotropic drugs, including haloperidol,[130,131,132] thiothixene,[133,134] benzoctamine,[135] doxepin,[136,137] and amoxapine.[138] Goldstein with his collaborator Benjamin Brauzer was first to use "symptomatic volunteers" in clinical investigations with psychotropics.[139]

George M. Simpson contributed to the clinical characterization of several antipsychotic and antidepressant drugs.[140,141] The wide range of neuroleptics he studied included fluphenazine,[142] haloperidol,[143] thiothixene,[144] oxipendyl,[145] prothipendyl,[146] molindone,[147] clozapine,[148] risperidone,[149] and many other drugs. In collaboration with Thomas Cooper, he explored the relationshp between plasma levels and clnical response. (See Cooper, Volume 5); and with Angus, he developed an extrapramidal symptom rating scale (ESRS) that was to become one of the standard instruments in the evaluation of antipsychotic drugs.[150] He also developed, in collaboration with Lee, Zuobolc and Gardos, (See Gardos in this Volume), a severity scale for tardive dyskinesia.[151] Simpson was among the first to report on withdrawal effects after discontinuation of treatment with phenothiazines in schizophrenia.[152] (See also Simpson, Volume 9).

George Gardos collaborated with Simpson on the development of the severity scale for **tardive dyskinesia** (TD.) Focusing on late neurological side effects of neuroleptics, he found an interaction between drug and disease related factors in the pathogenesis of TD.[153,154,155] In his early research, Gardos found that not all benzodiazepnes increased hostililty,[156] and that the therapeutic profile of thiothixene was different in low than in high doses.[157]

Two of the interviewees, Kane and Lieberman were intensively involved in research with **atypical antipsychotics** in treatment of schizophrenia. *John M. Kane* led the multicenter clinical investigations in which clozepine was found effective in some schizophrenic patients refractory to treatment with chlorpromazine[158] and haloperidol.[159] He was instrumental in the registration of clozapine in the United States. Kane has also contributed to verification of the efficacy of maintenance treatment with neuroleptics in schizophrenia.[160]

Jeffrey A. Lieberman, a collaborator of Kane in the 1980s, led the team which showed that response to a methylphenidate challenge[161] could predict early relapse in maintenance treatment of schizophrenic patients.[162] Lieberman was also principal investigator of the Clinical Antpsychotic Trials of Intervention Effectveness (CATIE), which conclusively demonstrated that "atypical neurleptics," offered a different side effect profile from typical neuroleptics but no advantages in terms of efficacy and therapeutic profile in the treatment of schizophrenia.[163]

Five of the interviewees, Bowden, Uhlenhuth, Kocsis, Winokur and Wheatley, were involved in research related to the **therapeutic profile** of drugs already in clinical use. *Charles C. Bowden* in the 1990s demonstrated that valproate semisodium (divalproex,) an anticonvulsant, had comparable efficacy to lithium, the standard mood stabilizer in the treatment of mania[164] and bipolar disorder.[165] He was instrumental in the registration of divalproex for the treatment of bipolar disorder in the United States.

Eberhard H Uhlenhuth, contributed to research which showed that olanzapine, an atypical neuroleptic for the treatment of schizophrenia, and moclobemide, a MAO-A inhibitor for the treatment of depression, might have a place in the treatment of panic disorder.[166,167] He also contributed to research which showed`that escitalopram, a selective serotonin re-uptake inhibitor for the treatment of major depression, might be useful in depressive symptoms of bereavement.[168] Uhlenhuth was first, in the late 1950s, to conduct a placebo and standard controlled clinical trial with meprobamate in patients with anxiety symptoms.[169] During the 1980s and 1990s, in collaboration with Mitchell Balter, he extended the scope of epidemiological research by surveying experts' judgments about the use of psychotropic drugs including benzodiazepines .[170,171,172]

James H. Kocsis was first to demonstrate that some of the antidepressants used in the treatment of major depression, e.g., imipramine, desipramine and sertraline, had a favorable effect on social functionig in patients with "dysthymia."[173,174,175]

Andrew Winokur s discovery in the 1970s that the thyrotropine releasing hormone (TRH) is widely distributed in the brain,[176] coupled with the demonstration of its activating effect, led to the hypothesis that TRH, like a thermostat, regulates arousal.[177] It led also to the possible extension of therapeutic indications for the substance.[178] (See Prange and Whybrow, Volume 5). Winokur was a member of the team which demonstrated the effectiveness of modafinil in controlling the excessive sedation of narcolepsy.[179]

David Wheatley was first to organize a general practice network for clinical investigations with psychotropic drugs.[180] He contributed to the clinical chracterization, as well as to the detection of special problems encountered with antidepressnats,[181,182] hypnotics,[183,184,185] anxiolytics,[186] and cognitive enhancers[187] in primary care.

At the heart of **psychopharmacological research** is the identification of psychiatric populations which are sufficiently homogeneous for studying the pathophysiology and neurochemical underpinning of the condition. Three of the interviewees, Klein, Quitkin and Schatzberg, were involved in such research. Based on responsiveness to imipramine, which he referred to later as "pharmacological dissection,"[188,189,190] *Donald F. Klein* in the early 1960s, identfied a population within the anxiety disorders that was characterized by recurent anxiety attacks.[191,192,193] He used the term "panic disorder," as a label for this population, and the term was adopted into DSM-III as an Axis I diagnosis. In the 1980s, Klein and his associates found that panic attacks could be triggered by increase of carbon dioxide in arterial blood flow,[194,195] leading to Klein's postulation that "panic diosrder" is a "false suffocation alarm".[196] (See also Klein, Volume 9) .

Frederic Quitkin, a disciple of Klein, corroborated in the late 1980s and early 1990s the diagnostic concept of "atypical depression," a population, identified on the basis of responsivenss to iproniazid. [197,198,199] He also verified the advantages of phenelzine over imipramine in that diagnosis [200,201,202]

Based on findings which indicated an upregulated hypothalmic-pituitary-adrenal axis with excessive glucocorticoid production in depressed patients with delusions, *Alan F. Schatzberg* in the mid-1980s advanced a corticosteroid/dopamine hypothesis for psychotic depression. He also demonstrated that administration of glucocrticoids produced "cognitive changes," similar to those seen in depression.[203] To block the effect of glucocorticoids Schatzberg suggested the administration of mifiprestone, an antagonist in high doses of low afinity glucocorticoid receptors.[204] It remains to be seen whether glucocorticoid receptor blockers have an effect on depression.

Interviewees included in Volume 4 entered the field at different stages in the developent of psychopharmacology. Hence the transcripts cover fifty years of history, from uncontrolled single center clinical studies to multicenter clinical investigation using power statistics. With the development of clinical methodology, evidence-based findings replaced testimonials about the clinical effects of psychotropic drugs. As the armamentarium of psychotropic drugs with demonstrated efficacy grew, it came to include first the anxiolyics and antidepressants, then the mood stabilzers and ultmately the cognitive enhancers. Yet, in spite of the steadily increasing number of available psychotropic drugs for psychiatric disorders, none of the newer drugs so far have shown different therapeutic efficacy than those already available, and clinical methodology has not advanced to determine differential thepeutic profiles.

Jerome Levine, the editor of this volume was one of the architects of the methodology used in clinical investigations with psychotropic drugs. Barry Blackwell, (see Blackwell in this Volume,) who contributed the Dramatis Personae, is a distinguished researcher in the field. He was first, in 1970, to record, in collaboration with Frank Ayd (See Volumes 1, 9, & 10) the story of the first pioneers in biological psychatry.[205] He is also editor of Volumes 7 and 9 of this series. The list of Abbreviations was contributed by Laura Hill from ACNP's Executive Office.

REFERENCES

1 Macht D. Contributions to psychophamacology. Bull Hopkins Hosp 1920; 31: 167-73.
2 Ban TA. Neuropsychopharrnacology and the history of pharmacotherapy in psychiatry. A review of developments in the 20th century. In: Ban TA, Healy D, Shorter E, editors. Reflections on Twentieth Century Psychopharmacology. Budapest: Animula; 2006; 69-720.
3 Ban TA. The role of serendipity in drug discovery. Dialogue in Clinical neuroscience 2006; 335-44.

4 Ban TA. Fifty years chlorpromazine. A historical perspective. Neuropsychiatric Disease and Treatment 2007; 3: 483-8.

5 Freyhan F. Selection of patients from the clinical point of view. In: Cole JO, Gerard RW, editors. Evaluation of Pharmacotherapy in Mental Illness. Washington: National Academy of Sciences; 1959. p. 372-89.

6 Angst J, Battegay R, Bente D, Cornu F, Dick P, Engelmeier MP, Hermann H, Henrich K, Hippius H, Pöldinger W, Schmdlin P, Schmitt W, Weis P. On the Proceedings of German and Swiss Association for the study of psychiatric documentation. Schweiz Arch Neurol Nerochir Psychiat 1967; 100: 207-11 (In German).

7 Angst J, Battegay R, Bente D, Berner P, Broeren W, Cornu F, Dick P, Engelmeier MP, Heimann H, Heinrich K, Helmchen H, Hippius H, Lukács G, Pöldinger W, Schmidlin P, Schmitt W, Weis P. Clinical documentation of psychopharmacology. (Association for Methodology and Documentation in Psychiatry.) In: Cerletti A, Bové FJ, editors. The Present Status of Psychotropic Drugs . Amsterdam: Excerpta Medica; 1969. p. 361-5. (In French.)

8 Angst J, Battegay R, Bente D, Berner P, Broeren W, Cornu F, Dick P, Engelmeier MP, Heimann H, Helmchen H, Hippius H, Pöldinger W, Schmidlin P, Schmitt W, Weis P. The documentation system of the Association for Methodology and Documentation in Psychiatry (AMP.) Arzneim Forsch 1969; 19: 399-405. (In German.)

9 Bente D, Feder J, Siegordner K. A computer program for interregional storage and statistical evaluation of AMP data. Arzneim Forsch 1970; 20{ 913-5. (In German.)

10 Scharfetter C. The AMP System. Berlin: Springer; 1971. (In German)

11 AMDP. Das`AMDP System Manual zur Dokumentation psychiatrischer Befunde. 8, bearbeitete Auflage. Gottingen: Hogrefe; 2007.

12 Ban TA, Lehmann HE, Galvan L, Pecknold JC, Climan M. A transcultural study with Comparison of two assessment methods. Current Therapeutic Research 1974; 16: 971-89.

13 Scharfetter C. The AMP System. 2nd edition. Berlin: Springer; 1972. (In German.)

14 Ban TA. The AMP System in Enlish. In: Deniker P, Radouco-Thomas C, Villeneuve A, editors. Proceedings of the Xth Congress CINP. London: Pergamon Press; 1978. p. 1575-9.

15 AMDP. Das AMDP System Manual zur Dokumentation psychiatrischer Befunde . 3, Auflage. Berlin: Springer; 1977.

16 Guy W, Ban TA. The`AMDP System. Heidelberg: Springer; 1982.

17 Bobon D. Conceptual and semantic problems raised by the French translation of the AMP Psychopathology Scale. In: Deniker P, Radouco-Thomas C, Villeneuve A, editors. Proceedings of the Xth Cogress CINP. London: Pergamon Press; 1978. p. 1583-8.

18 Bobon D, Saarma J. Summary of the First Workshop on Translation of the`AMP System. In: Deniker P, Radouco-Thomas C, Villeneuve A, editors. Proceedings of the Xth Congress CINP. London: Pergamon Press; 1978. p. 1555-6.

19 Bobon D, Baumann U, Angst J, Helmchen H, Hippius H, editors. AMDP-System in Pharmacopsychiatry. Basel: Karger; 1983.

20 Guy W, Ban TA. The AMDP and NCDEU /BLIPS`` Systems: similarities and differences. In: Bobon D, Baumann U, Angst J, Helmchen H, Hippius H, editors. AMDP-System in Pharmacopsychiatry. Basel: Karger; 1983. p. 185-192.

21 McGlashanT. The Documentation of Psychotropic Drug Trials. Washington: National Institute of Mental Health. DHW Publication No (HSM) 73-9038; 1973.

22 Guy W, Bonato R. Manual for the ECDEU Assessment Battery.Washington: DHEW Pub No (ADM) USGPO; 1970.

23 Guy W. Manual for the ECDEU Assessment Battery. Revised. Washington: DHEW Pub No (ADM) USGPO; 1976.

24 Ban TA, Wilson WH. Multicenter clinical trials: methodological aspects. Mod. Probl Pharmacopsychiatry 1981; 16: 9-20. .

25 Wilcoxon WH, Ban TA. Repeated measures Latin-square designs in clinical pharmacology. Meth and Find Clinical Pharmacol 1982; 41: 37-42.

26 American Psychiatric Association. Diagnostic and Statistical Manual First Edition (DSM-I). Washington: American Psychiatric Association; 1952.

27 World Health Organization. International Classification of Diseases. 6th edition. Geneva: World Health Organization; 1949.

28 World Health Organization. International Classification of Diseases. 7th edition. Geneva: World Health Organization; 1955.
29 World Health Organization. International Classification of Diseases. 8th edition. Geneva: World Health Organization; 1965.
30 American Psychiatric Association. Diagnostic and Statistical Manual Second Edition (DSM-II). Washington: American Psychiatric Association; 1968.
31 West ED,Dally PJ. Effects of iproniazid in depressive syndromes. Br Med J 1959; 1: 1491-99.
32 Sargant W, Dally PJ. Treatment of anxiety states by antidepressant drugs. Br Med.J 1962; 1:609.
33 Roth M. The phobic-anxietydepersonalization syndrome. Proc R Soc Med 1958; 52: 587-95.
34 Hollender M, Ban TA. Ejaculatio retarda`due to phenelzine. Psychiatric J Univ of Ottawa 1979; 6: 233-4.
35 Wing L, Bramley C, Hailey A, Wing KJ. Camberwell cumulative psychiatric case register. Part I: Time and methods. Soc Psychiatry 1968; 3: 116-23.
36 Ottoson JO, PerrisC. Multidimensional classification of mental disorders. Psychol Med 1973; 3: 238-43.
37 Helmchen H. Schizophrenia: Diagnostic concepts in the ICD-8. Br J Psychiatry 1975; 10: 10-8.
38 Helmchen H. Multiaxial systerms of classification. Types of axes. Acta psychiat Scand 1980; 61: 43-55.
39 Strauss JS. A comprehensive approach to psychiatric diagnosis. Am J Psychiatry 1975; 132: 1193-7.
40 Amerian Psychiatric Association. Diagnostic and Statistical Manual of Psychiatric Disorders. Third Edition. (DSM-III.)Washington: American Psychiatric Association; 1980.
41 Robins E, Guze SB. Establishment of diagnostic validity in psychiatric illness. Am J Psychiatry 1970; 125: 983-7.
42 Fleiss JL, Spitzer RL, Endicott J, et al. Quantification of agreement in multiple psychiatric diagnosis. Arch Gen Psychiatry 172; 26: 168-71.
43 Garrison FH. A History of Medicine.Philadelphia: Fourth edition. Philadelphia: Saunders; 1960. p. Saunders; 1960. p. 79-120.
44 Mezzich J. Multiaxial diagnostic systems in psychiatry. In: Kaplan HE, Freedman AM, Sadock BJ, editors. Comprehensive Textbook of Psychiatry . Baltimore: Williams & Wilkins; 1980. .
45 American Psychiatric Association. Diagnostic and Statistical Manual of Psychiatric Disorders. Third Edition. Revised. (DSM-III-R.) Washington: American Psychiatric Association; 1987.
46 American Psychiatric Association. Diagnostic and Statistical Manual of Psychiatric Disorders. Fourth Edition. (DSM-IV.) Washington: American Psychiatric Association; 1994.
47 Ban TA. From DSM-III to DSM-IV: Progress or standstill. In: Franzek E, Ungvari GS, Rűther E, Beckmann H. Progress in Differentiated Psychopathology. Würzburg: International Wernicke-Kleist-Leonhard Society; 2000. p. 1-11.
48 National Institute of Mental Health. Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment of acute schizophrenia: Effectiveness Arch Gen Psychiatry 1964; 10: 246-61.
49 National Institute of Mental Health. Psychopharmacology Service Center Collaborative Study Group Differences in clinical effects of three phenothiazines in “acute schizophrenia.” Dis Nerv System 1967; 28: 169-81
50 Goldberg SC, Klerman GL, Cole JO. Changes in schizophrenic psychopathology and ward behavior as a function of phenothiazine treatment. Brit J Psychiat 1965; 111: 120-33.
51 Klerman GL, ColeJO. Clinical pharmacology of imipramine and related antidepressant compounds. Pharmacol Rev 1965; 17: 101-41.
52 Levine J, Schooler N. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacology Bulletin 1986; 22: 343-81.
53 Ludwig A, Levine J, Stark L, Lazar R. A clinical study of LSD treatment of alcoholism. Am J Psychiatry 1969; 12: 59-69.
54 Ludwig A, Levine J, Stark L. LSD and Alcoholism. Springfield: Thomas; 1970.
55 Hoffer A, Osmond H. A New Hope for Alcoholics. New York: University Books; 1968. p. 1-252.
56 Elkin I, Parloff MB, Hadley SW, Autry JH. NIMH treatment of depression. Collaborative research program. Archives of General Psychiatry 1985; 42: 305-16.
57 Lorr M, Jenkins RL, Holsopple JA. Multidimensional scale for rating psychiatric patients. (MSRPP.) VA Tech Bull 1953; 10:507-8

58 Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962; 10: 799-812
59 Overall JE, Spiegel DK.Concerning least squares analysis of experimental data. Psychological Bulletin 1969; 72: 311-22.
60 Overall JE, Klett JC. Applied Multivariate Analysis. New York: McGrow Hill; 1971
61 Honigfeld G, Klett C. The Nurses Observation Scale for Inpatient Evaluation (NOSIE) : A new scale for measuring improvement in chronic schizophrenia. J Clin Psychol 1965; 21: 65-71.
62 Casey JF, Lasky JJ, Klett CJ, Hollister LE. Treatment of schizophrenic reactions with phenothiazine derivatives. Amer J Psychiatry 1960; 117: 97-105
63 Lorr M, Klett CJ. Inpatient Multidimensional Psychiatric Scale. IMPS. Palo Alto: Consulting Psychologists Press; 1975.
64 Lorr M, Klett CL. Inpatient Multidimensional Psychiatric Scale Manual (IMPS) Palo Alto: Consulting Psychologists Press; 1962
65 McNair DM, Lorr M, Droppleman LF. Manual for the Profile of Mood States. POMS. San Diego: Educational and Industrial Testing Services; 1971
66 Raskin A. Adverse reactions to phenelzine: Results of nine hospitals depression study. The Journal of Clinical Pharmacology and New Drugs 1972; 12: 22-5.
67 Raskin A, Schulterbrandt J, Reatig N, McKeon JJ. Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives.. J. Nerv. Ment. Dis 1969; 148: 87–98.
68 Raskin A, Crook T. The endogenous–neurotic distinction as a predictor of response to antidepressant drugs. Psychological Medicine 1976; 6: 59-70.
69 Vinar O, Vana J, Grof S. Rating scale FKP. Activ nerv Super 1966; 8: 405-420.
70 Vinar O. Clinical change as measured by the FKP and FK rating scales. In: Boissier JR, Hippius H, Pichot P, editors. Neuropsychopharmacology. Amsterdam/New York: Excerpta Medica/American Elsevier Publishing Company Inc: 1975. p. 48-67.
71 Vinar O. Psychopharmacology research ward. Ten years experience. Int Pharmacopsychiatry 1976; 11: 32-42.
72 Vinar O. My memories of early psychotropic drug development. In: Ban TA, Healy D, Shorter E, editors. The Rise of Psychopharmacology and The Story of CINP. Budapest: Animula; 1998, p. 229-34...
73 Rickels K. Non-specific factors in drug therapy of neurotic patients. In: Rickels K, editor. Non-Specific Factors in Drug Therapy. Springfield: Charles C. Thomas; 1968. p. 3-26.
74 Rickels K, Cattell RB, Weise C, Gray B, Yee R, Mallin A, Aaronon HG. Controlled` psychopharmacological research in private psychiatric patients. Psychopharmacologia 1966; 9: 288-306.
75 Rickels K. Drugs in the treatment of neurotic anxiety and tension. Controlled studies. In: Solomon P, editor. Psychiatric Drugs. New York: Grune & Stratton; 1966. p. 223-37.
76 Rickels K, Downing RW, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone and diazepam. Arch Gen Psychiat 1993; 50: 884-95.
77 Hogarty GE. Goldberg SC, Schooler NR, Ulrich R F. Drug and socio-therapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. Arch Gen Psychiatry 1974; 31: 603-8.
78 Hogarty GE, Goldberg SC, Schooler NR. Drug and sociotherapy in the aftercare of schizophrenic patients. III. Adjustment of non relapsed patients. Arch Gen Psychiatry, 1974; 31: 609-8.
79 Hogarty GE. Personal Therapy for Schizophrenia and Related Disorders: A Guide to Individualized Treatment. New York: Guilford Press: 2002. p. 1-338
80 Schooler N, Hogarty G, Weissman M. Social Adjustment Scale II (SAS II) In: Hargraeve WA, Atkinson CC, Sorensen JE, editors. Resource Materials for Community Mental Health. Washington: National Institute of Mental Health (ADM 70-328); 1979. p 290-3.
81 Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey PD, Kopala L, McGorry PD, Van Hove I, Eerdekens M, Swyzen W, De Smedt G; Early Schooler N, Working Group. Risperidone and haloperidol in the first-episode psychosis a long –term randomized trial. Am J Psychiatry 2005;162: 947-53.
82 Schooler N. New antipsychotic medications : strategies for evaluation and selected findings. Schzophrenia Research 1997; 27: 249-59.
83 Katz MM, Lyerly SB. Methods of measures of adjustment of social behavior in the community. I. Rationale, description, discriminative validity, and scale development. Psychological Reports 1963; 13: 503-35

84 Katz MM, Itil TM. Video methodology for research in psychopathology and psychopharmacology. Arch Gen Psychiatry 1974; 31: 204-10
85 Katz MM, Wetzler S, Koslow SH, Secunda S. Video methodology of the psychopathology and treatment of depression. Psychiatric Annals 1989; 19: 372-81
86 Katz MM, Koslow SH, Maas JW, et al. The timing, specificity and prediction of tricyclic drug effects in depression. Psychological Medicine1987; 17: 297-309
87 Katz MM, Houston JP, Brannan S, Bowden CL, Berman N, Swann AC, Frazer A. A multidimensional behavioral method for measuring onset and sequence of the clinical action of antidepressants. Int J Neurosychopharmacol 2004; 7: 471-9
88 Katz M, Tekell J, Bowden CL, Brannan S, Houston JP, Berman N, Frazer A. Onset and early behavioral effects of pharmacologically different antidepressants and placebo in depression. Neuropsychopharmacology 2004; 7: 566-70.
89 Paykel ES. Recent life events in the development of depressive disorders: a controlled study. Arch Gen Psychiatry 1969; 21: 253-60.
90 Paykel ES Classification of depressed patients: A cluster analysis derived grouping. The British Journal of Psychiatry 1971; 118: 275-88.
91 Rowas PR, Paykel ES, Parker RR. Phenelzine and amitriptyline effects on symptoms of neurotic depression. The British Journal of Psychiatry 1982; 40: 475-83
92 Paykel ES Continuation and maintenance therapy in depression. British Medical Bulletin 2001; 57: 145-59.
93 Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. Brit Med J 1970; 2: 49-43.
94 Blackwell B. Hypertensive crisis due to MAOI. Lancet 1963; 2: 849-51.
95 Blackwell B, Marley E, Price J, Taylor D. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. Br J Psychiatry 1967; 113: 349-65.
96 Blackwell B. The cheese story. In Ban TA, Healy D, Shorter E, editors. The Rise of Psychopharmacology and the Story of CINP. Budapest: Animula; 1998. p. 87-90..
97 Sheehan DV, Lecrubier Y, Amorim P, Janays J, Weiller E, Herguela T, Baker R, Dunbar GC. The MINI International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59 (Supplement 20): 22-33
98 Lecrubier Y. Physical components of depression and psychomotor retardation. J Clin Psychiatry 2006; 67 (Supplement 6): 23-6.
99 Kapur S, Lecrubier Y, editors. Dopamine in the Pathophysiology of Schizophrenia. London: Martin Dunitz; 2003
100 Carlsson A, Lecrubier Y, editors Dopamine Research in Schizophrenia . London: Taylor & Francis; 2004.
101 St.Laurent, Cahn C, Ban TA. Treatment of psychiatric patients with a phenothiazine derivative (prochlorperazine) with special reference to after care. Am J Psychiatry 1962; 118: 938-40
102 Ban TA, Schwarz L. Systematic studies with levomepromazine. Journal of Neuropsychiatry 1963;5:112-7.
103 Ban TA, Papathomopoulos E, Schwarz L. Clinical studies with thioproperazine (Majeptil.) Comprehensive Psychiatry 1962; 3: 284-91.
104 Ban TA. The butyrophenones in psychiatry. In Lehmann HE, Ban TA, editors. Te Butyrophenones in Psychiatry. Montreal: Quebec Psychopharmacological Research Association : 1964. p. 120-34.
105 Ban TA, Ferguson K, Lehmann HE. The effect of clopenthixol on chronic psychiatric patients. Am J Psychiatry 1963; 119: 984-5..
106 Lehmann HE, Ban TA. Studies with thioxanthenes. In: Ban TA, Lehmann HE, editors The Thioxanthenes. Basel: Karger: 1949. p.85-9.
107 Ban TA. Psychopharmacology of Thiothixene. New Yourk: Raven Press; 1978.
108 Chouinard G, Lehmann HE, Ban TA. Pimozide in the treatment of chronic schizophrenic patients. Current Therapeutic Research 1970; 12: 598-603.
109 Chouinard G, Lehmann HE, Ban TA, Ananth JV. Fluspiriline in the treatment of chronic schizophrenic patients. Current Therapeutic Research 1970; 12: 604-8.
110 Ban TA, Lehmann HE. Clinical trial with desmetylimipramine , a new antidepressant. Canadian Psychiatric Association Journal 1962; 86: 1020-1.

111 Ban TA. Trimipramine in psychiatry. In Lehmann HE, Berthiaume M, Ban TA,. editors. Montreal: Quebec Psychopharmacologica Research Association; 1965.
112 Ban TA. Depression and the Tricyclic Antidepressants. Montreal; Ronalds Federated; 1974.
113 Ban TA. Introduction to the Psychopharmacology of Doxepin.Montreal: Pfizer; 1977.
114 Ban TA. Psychopharmacology of Depression. Basel: Karger; 1981..
115 Ban TA, Amin M, Nair NPV, Engelsman F. Comprehensive clinical studies with trazodone in Canada. In: Ban TA, Silvestrini B, eds. Trazodone. Modern Problems in Pharmacopsychiatry Vol 9. Basel: Karger; 1974, p. 110-26.
116 Ban TA, Gaszner P, Aguglia E, Batista R, Castillo A, Lipcsey A, Macher J-P, Torres-Ruiz A, Vergara L. Clinical efficacy of reboxetine: a comparative study with desipramine, with methodological considerations. Human Psychopharmacology 1998; 13 (Supplement): S29-S39.
117 Ban TA, St.Jean A. The effect of phenothiazines on the electrocardiogram . CMAJ 1964; 91: 537-40.
118 Ban TA, Lehmann HE, Saxena BM. A conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. Canadian Psychiatric Association Journal 1970; 15: 301-8.
119 Pethö B, Ban TA. DCR Budapest-Nashville in the Diagnosis and Classification of Functional Psychoses. Psychopathology 1988; 21: 153-240.
120 Ban TA. CODE DD Composite Diagnostic Evaluation of Depressive Disorders. Brentwood: JM Productions; 1989.
121 Ban TA. Clinical pharmacology and Leonhard's classification of endogenous psychoses. Psychopathology1990; 23: 331-8.
122 Gallant D, Bishop M, Timmons E, Steele CA. A comparative evaluation of triperidol (R2498) : a new potent psychopharmacologic agent. Curr. Ther Res 1963; 5: 463-6..
123 Gallant DM, Bishop MP. IM thiothixene and trifluoperazine. Psychopharmacol Bull 1969; 5:46-8.
124 Gallant DM, Bishop MP, Shelton W. A preliminary evaluation of P-4657B : a thoxanthene derivative. Am J Psychiatry 1966; 123: 345-6.
125 Gallant DM, Bishop MP. Cinanserin (SQ 10,643) : a preliminary evaluation in chronic schizophrenic patients. Curr Ther Res 1968; 10:461-3.
126 Gallant DM, Mielke DH, Spirtes MA, Swandon WC, Bost R. An efficacious long-acting oral antipsychotic compound. Am J Psychiatry 1974; 133: 609-702.
127 Gallant DM, BishopMP, Guerrero-Figureoa R, Selby M, Phillips R. Doxepin vs diazepam a controlled evaluation in chronic alcoholic patients. J Clin Phramacol J New Drugs 1969; 9: 57-65
128 Dillenkoffer RL, George RB, Bishop MP, Gallant DM. Electrocardiographic evaluation of thiothixene: a double-blind comparison with thoridazine. Adv Biochem. Psychophamacol. 1974; 9: 487-95.
129 Gallant DM, Force R, editors. Legal and Ethical Issues in Human Research and Treatment: Psychopharmacology Considerations. New York: Spectrum Publishing; 1978.
130 Goldstein BJ. Haloperidol in controlling the symptoms of acute psychosis: Part I. A preliminary investigation. Current Therapeutic Research. 1966; 8: 231-4.
131 Goldstein BJ, Clyde DJ. Haloperidol in controlling the symptoms of acute psychosis. Part II. A double-blind evaluation of haloperidol and trifluoperazine. Current Therapeutic Research 1966; 8:235-9.
132 Goldstein BJ, Brauzer B, Clyde DJ, Caldwell JM. The differential prediction of response to haloperidol and perphenazine. Psychosomatics. 1969;10: 193-7.
133 Goldstein BJ, Weiner D, Banas F. Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients. Lehmann HE, Ban TA, editors. The Thioxanthenes. Modern Problems in Pharmacopsychiatry, Vol. 2. Basel: Karger; 1969. p. 45-52.
134 Goldstein BJ, Brauzer B. Thiothixene in the treatment of mixed anxiety and depression. J Clin Pharmacol 1973; 13: 167-73.
135 Goldstein BJ, Weiner DM. Comparative evaluation of benzoctamine and diazepam in treatment of anxiety. Journal of Clinical Pharmacology 1970; 10:194-8.
136 Goldstein BJ, Pinosky DG. Clinical evaluation of doxepin in anxious depressed outpatients. Psychosomatics 1969; 10:37-8.
137 Goldstein BJ, Brauzer B, Steinbook RM, Jacobson AF. Psychotropic drug treatment of mixed anxiety and depression in non-psychiatric office patients: expected and unexpected findings – comparing doxepin , chlordiazepoxide and placebo. South Med J 1973; 66: 892-7.
138 Goldstein BJ, Dominguez RA, Weiss BL. Amoxapine in psychotic depression. Journal of Clinical Psychiatry 1985; 3: 14-6.

139 Goldstein BJ, Brauzer B. Symptomatic volunteers – A new patients' treatment model. In: Vinar O, Votava Z, Bradley PB, editors. Advances in Neuropsychopharmacology Amsterdam/Prague: North Holland Publishing Company/Avicenna Czechoslovak Medical Press; 1971. p. 375-88.
140 Kline NS, Simpson G, Brodie BB. The clinical application of desmethylimipramine. : A new type of antidepressant drug. International Journal of Neuropharmacology 1962; 1: 55-60.
141 Simpson GM, Amin M, Angus JWS, Edwards JG, Go SH, Lee JH. Role of antidepressants and neuroleptics in the treatment of depression.`Arch Gen Psychiatry27: 337-45.
142 Simpson GM, Amin m, Kunz E, McCafferty FV. Studies on a second long-acting fluphenazine . Am J Psychiatry 1965; 121: 784-7.
143 Simpson GM, Angus JWS, Edwards JG. A controlled study of haloperidol in chronic schizophrenia. Current Therapeutic Research 1967; 407: 407-12.
144 Simpson , GM, Iqbal J. A preliminary study of thiothixene in chronic schizophrenics. Current Therapeutic Research 1965; 7: 697-700.
145 Simpson GM, Angus JWS. A preliminary study of oxipendyl in chronic schizophrenia. Curr Ther Res 1967; 9: 225-8.
146 Simpson GM, Angus JWS. A preliminary study of prothipendyl in chronic schizophrenia. Curr Ther Res 1967; 9: 265-8.
147 Simpson GM, Krakow L. A preliminary study of molindone (IN 1733A) in chronic schizophrenia. Curr Ther Res 1968; 19: 41-6.
148 Simpson GM, Varga E. Clozapine – a new antipsychotic agent. Current Therapeutic Research 1974; 18: 679-81.
149 Simpson GM, Lindermayer JP. Extapyramidal symptoms in patients treated with risperidone. J Clin Psychopharmacol 1997; 17: 194-201.
150 Simpson GM, Angus JW A rating scale for extrapyramidal side effects. Acta Psychiatrica Scandinavica. 1970; 212 (Supplement): 11-19.
151 Simpson GM, Lee JH, Zoubolc B, Gardos G. A rating scale for tardive dyskinesia. Psychopharmacologia 1978; 64: 171-9
152 Simpson GM, , Amin M, Kunz E. Withdrawal effect of phenothiazines. Compr Psychiat 1965; 6: 347-51.
153 Gardos G, Cole JO, La Brie RA. Drug variables in the etiology of tardive dyskinesia. Progress in Neuro-Psychopharmacology & Biological Psychiatry 1977; 1: 147-54.
154 Gardos G, Cole JO. Tardive dyskinesia and affective disorder. In: Gardos G, Casey DE, editors. Tardive Dyskinesia and Affective Disorders. Washington: American Psychiatric Press; 1984. p. 69-80.
155 Gardos G, Casey DE, Perenyi A, Cole JO, Kocsis E, Arato M, Conley C, Samson J. Ten year follow-up study of tardive dyskinesia and drug-induced Parkinsonism. Psychiatria Hungarica` 1994; 9: 137-45.
156 Gardos G, DiMascio A, Salzman C, Shader RI. Differential action of chlordiazepoxide and oxazepam on hostility. Arch Gen Psychiatry 1968; 18; 757-60.
157 Gardos G, Cole JO. The dual action of thiothixene. Arch Gen Psychiatry 1973; 29: 222-5.
158 Kane JM, Honigsfeld G, Singer J, Meltzer H et al. Clozaril for the treatment resistant schizophrenic: A double-blind comparison versus chlorpromazine/benztropine. Archives of General Psychiatry 1988; 45: 789-96
159 Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht D, Baker RW, Wirshing DA, Safferman A, Ganguli R, Bronstein M, McMenniman M. Clozapine and haloperidol in moderately refractory schizophrenia: a six months randomized and double-blind comparison. . Arch Gen Psychiatry 2001; 58: 965-72
160 Kane JM, Quitkin F, Rifkin A, Ramos–Lorenzi JR, Nayak D. Fluphenazine versus placebo in patients with remitted acute first episode schizophrenia. Arch Gen Psychiatry 1982; 39: 70-3.
161 Janowsky D, El-Yousef MK, Davis JM, et al. Provocation of schizophrenic symptoms by intravenous administration of methylphenidate .Archives of General Psychiatry 1973; 28: 185-91
162 Lieberman JA, Kane JM, Gadaleta D, Brenner R, Lesser MS, Kinon B. Methylphenidate challenge as predictor of relapse in schizophrenia. Am J Psychiatry 1984; 141: 633-8
163 Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Kiefe RSE, Davis SM, Davis CI, Lebowitz GD, Severe J, Hsiao JK, for the Clinical Antipsychotic Trials of the Intervention Effectiveness Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The New England Journal of Medicine 2005; 353: 1209-23.

164 Bowden L, Brugger AM, Swann AC, et al Efficacy of divalproex vs lithium vs placebo in the treatment of mania. JAMA 1994; 271: 918-24.
165 Bowden CL, Calabrese JR, McElroy SL, et al. A randomized placebo-controlled 12-week trial of divalproex and lithium in the treatment of psychiatric patients with bipolar disorder. Arch Gen Psychiatry 2000; 57: 481-90.
166 Hollifield M, Thompson PM, Ruiz JE, Uhlenhuth EH. Potential effectiveness and safety of olanzapine in refractory panic disorder. Depress Anxiety 2005; 21: 33-40.
167 Ross DC, Klein DF, Uhlenhuth EH. Improved statistical analysis of moclobemide dose effects on panic disorder treatment. Eur Arch Psychiatry Clin Neurosci 2010; 260: 243-8.
168 Hensley PL, Slonimski CK, Uhlenhuth EH, Clayton PJ. Escitalopram: an open label study of bereavement related to depression and grief. J Affect Disord 2000; 113: 142-9.
169 Uhlenhuth EH, Canter A, Neustadt JO, Payson HE The symptomatic relief of anxiety with meprobamate, phenobarbital and placebo. Am J Psychiatry 1959; 115: 905-10, 1959
170 Uhlenhuth, EH, Balter MB, Mellinger GD. Clinical variables in pharmacoepidemiology. J Psychiatr Res 1993; 27 (Supplement.1): 89–95.
171 Uhlenhuth EH, Balter MB, Ban TA, Yang K. Trends in recommendations for the pharmacotherapy of anxiety disorders by an international expert panel. 1992-1997. European Psychopharmacology 1999; 9(Supplement 6): S393-S398.
172 Uhlenhuth EH, Balter MB, Ban TA, Yang K. International study of expert judgment on therapeutic use of benzodiazepines and other therapeutic medications: IV. Therapeutic dose dependence and abuse liability of benzodiazepines in the long-term treatment of anxiety disorders. J Clin Psychopharmacol 1999; 19: 2S-29S
173 Kocsis JH, Frances AJ. A critical discussion of DSM-III dysthymic disorder. Am J. Psychiatry 1987; 144: 1534-42.
174 Freedman RA, Markowitz JC, Parides M, Kocsis JH. Acute response of social functioning in dysthymic patients with desipramine. J Affective Disorder 1995; 34: 85-8
175 Kocsis JH, Zisook S, Davidson J, Shelton R, Yonkers K, Hellerstein DJ, Rosenbaum J, Halbreich U. Double-blind comparison of sertraline, imipramine and placebo in the treatment of dysthymia . Psychosocial outcome measures. Am J Psychiatry 1997; 154: 390-5. .
176 Winokur A, Utiger RD. Thyrotropin releasing hormone: regional distribution in the rat brain. Science 1974; 185: 265-6.
177 Garyl KA, Sevarinol KA, Yarborough GG, Prange JJ, Winokur A The thyrotropin-releasing hormone (TRH) hypothesis of homeostatic regulation: implications for TRH-based therapeutics. The Journal of Pharmacology 2003; 305: 410-6
178 Szuba MP, Amsterdam JD, Fernando AT, Whybrow PC, Winokur A Rapid antidepressant response after nocturnal TRH administration in patients with bipolar I and bipolar II patients with major depression. J Clin Psychopharmacol 2005; 25: 325-30
179 US Modafinil Narcolepsy Multicenter Study Group. Randomized trial for the excessive daytime sedation of narcolepsy. Neurology 2000; 54: 1166-75.
180 Wheatley D. Research in general practice. In: Ban TA, Healy D, Shorter E, editors. The Rise of Psychopharmacolog and The Story of CINP. Budaes: Animla; 1998. p. 281-4.
181 Wheatley D. Drinamyl in depressive illness Br. Med J 1964; 15: 818-20
182 Wheatley D. Adrenergic drugs in depression. Arch Gen Psychiatry 1975; 32: 653-55.
183 Wheatley D. Psychopharmacology Of Sleep . London: Heinemann & Appleton Century Croft; 1981.
184 Wheatley D New hypnotic agents: clinical study in general practice Pharmacology, Biochemistry and Behavior 1988; 29: 811-3
185 Wheatley D. Insomnia in general practice: the role of temazepam in comparison with zopiclone. Acta Psychiatr Scandinavica 2007; 74: 142-8
186 Wheatley D. The Anxiolytic Jungle. Chichester: Wiley; 1990.
187 Wheatley D. Psychopharmacology of Cognitive and Psychiatric Disorders in the Elderly. London: Chapman & Hall; 1997.
188 Klein DF. Drug therapy a means of syndromal identification and nosological revision. In: Cole JO, Freedman AM, Friedhoff AJ, editors. Psychopathology and Psychopharmacology. Baltimore and London: The Johns Hopkins University Press; 1973. p. 143-60.
189 Klein DF. The pharmacological validation of diagnoses. In: Robins LN, Barret JE, editors. The Validity of Psychiatric Diagnoses. New York: Raven Press:1989. p. 203-217
190 Klein DF. The loss of serendipity in psychopharmacology. JAMA 2008; 299: 1063-5.

191 Klein DF, Fink M. Behavioral reaction patterns with phenothiazines. Archives of General Psychiatry 1962; 24: 449-59.
192 Klein DF. Delineation of two drug-responsive anxiety syndromes. Psychophramacologia 1964; 5: 397-408
193 Klein DF. Anxiety re-conceptualized Comprehensive Psychiatry 1980; 21: 411-27.
194 Papp LA, Martinez JM, Klein DF, Liebowitz MR, Fyer AJ, Hollander I, Gorman JM. Arterial blood changes in panic disorder and lactate-induced panic. Psychiatry Research 1989; 28: 171-80.
195 Papp LA, Klein DF, Gorman JM.. Carbon dioxide hypersensitivity, hyperventilation and panic disorder. Am J Psychiatry 1993; 150: 1149-57.
196 Klein DF. False suffocation alarms, spontaneous panics, and related conditions: an integrative approach. Ach Gen Psychiatry 1993; 50: 306-17.
197 Quitkin FM, Stewart JW, McGrath PJ, Liebowitz MR, Harrison WM, Tricamo E, Klein DF, Rabkin JG, Markowitz JS, Wager SG: Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. Am J Psychiatry 1988; 145:306-11.
198 Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Wager SG, Nunes E, Rabkin JG, Tricamo E, Markowitz J, Klein DF: Phenelzine and imipramine in mood reactive depressives: further delineation of the syndrome of atypical depression. Arch Gen Psychiatry 1989; 46:787-93
199 Quitkin FM, McGrath PJ, Stewart JW, Harrison W, Tricamo E, Wager SG, Ocepek-Welikson K, Nunes E, Rabkin JG, Klein DF. Atypical depression, panic attacks, and response to imipramine and phenelzine: a replication. Arch Gen Psychiatry 1990; 47 935-41.
200 Quitkin FM, Harrison W, Stewart JW, McGrath PJ, Tricamo E, Ocepek-Welikson K, Rabkin JG, Wager SG, Nunes E, Klein DF. Response to phenelzine and imipramine in placebo non-responders with atypical depression: a new application of the crossover design. Arch Gen Psychiatry 1991; 48:319-32.
201 Quitkin FM, Stewart JW, McGrath PJ, Tricamo E, Rabkin JG, Ocepek-Welikson K, Nunes E, Harrison W, Klein DF. Atypical depression: a subgroup of depressives with better response to MAOI than to tricyclic antidepressants or placebo. Br J Psychiatry 1993; 21: 30-34
202 Quitkin FM, Stewart JW, McGrath PJ, Nunes EV, Klein DF: The identification and validation of distinct depressive syndromes in a population-based sample of female twins. Arch Gen Psychiatry 1997; 54: 970-2.
203 Schatzberg AF, Rothschild AJ, Langlais PJ, Bird ED, Cole JO A corticosteroid/dopamine hypothesis for psychotic depression and related states. J Psychiatr Res 1985; 19:57–64
204 Rotschild AJ, Schatzberg AF. Diagnosis an and treatment of psychotic depression. In: Grunhaus L, Greden JF, editors. Severe Depressive Disorders. Washington: American Psychiatric Press; 1994. p. 195-207
205 Ayd FJ, Blackwell B. Discoveries in Biological Psychiatry. Philadelphia: JB Lippincott Company; 1970.

CONTENTS

ABBREVIATIONS

Prepared by Laura Bersacola Hill

AA	Alcoholics Anonymous
ACNP	American College of Neuropsychopharmacology
ACTH	adrenocorticotropic hormone
AD	Alzheimer's disease; antidepressant; After Date
ADAMHA	Alcohol, Drug Abuse and Mental Health Administration
ADHD	attention deficit hyperactivity disorder
AGP	Association for Geropsychiatry
AIMS	Abnormal Involuntary Movement Scale
AMA	American Medical Association
AMDP	Association for Methodology and Documentation in Psychiatry
AMP	adenosyl monophosphate
AMPT	alpha-methyl-p-tyrosine
ANCOVA	analysis of covariance
APA	American Psychiatric Association
ASI	Anxiety State Inventory
BA	bachelor of art
BAP	British Association of Psychopharmacology
BC	Before Christ
BLIPS	Biometric Laboratory Information Processing System
BPRS	Brief Psychiatric Rating Scale
BS	Bachelor of Science
BSS	bachelor of social science
BU	Boston University
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBASP	cognitive behavioral analysis system psychotherapy
CBT	cognitive behavioral therapy
CDZ	chlordiazepoxide
CCNT	College of the City of New York
CEO	chief executive officer
CET	cognitive enhancement therapy
CIA	Central Intelligence Agency
CINP	Collegium Internationale Neuro-Psychopharmacologicum
CNPRL	Central Neuropsychopharmacology Research Laboratory
CNS	central nervous system
CPZ	chlorpromazine
CRH	corticotrophin releasing hormone

CRO	clinical research organization
CSF	cerebrospinal fluid
CT	computerized tomography
CV	curriculum vitae
D	dopamine receptor
DA	dopamine; district attorney
DC	District of Columbia
DEA	drug enforcement agency
DRGs	diagnosis related groups
DSI	Depression State Inventory
DSM-III	Diagnostic and Statistical Manual Third Edition
DSM-III-R	Diagnostic and Statistical Manual Third Edition Revised
DSM-IV	Diagnostic and Statistical Manual Fourth Edition
DST	dexamethasone suppression test
DT	delirium tremens
ECDEU	Early Clinical Drug Evaluation Unit
EDTA	ethylenediaminetetraacetic acid
ECA	epidemiological catchment area
ECT	electroconvulsive therapy
EKG	electrocardiogram
ELSH	East Louisiana State Hospital
EPS	extrapyramidal signs
EQ	emotional quotient
ESRS	Extrapyramidal Symptom Rating Scale
FDA	Food and Drug Administration
FKD	Farmacologicka Kvantífikace Deprese (Czech)
FKP	Farmacologicka Kvantífikace Psychos (Czech)
FORTRAN	formula translation translator
FRG	Federal Republic of Germany
GAD	generalized anxiety disorder
GHQ	General Health Questionnaire
GI bill	serviceman re-adjustment act
GLMM	generalized linear mixed model
GP	general practitioner
GR	glycocorticoid receptor
GRCU	general clinical research unit
GW	George Washington University
HAM-A	Hamilton Anxiety Scale
HAM-D	Hamilton Depression Rating Scale
HMO	health maintenance organization
HPA	hypothalamic-pituitary adrenal axis

HVA	vanylmandelic acid
IBM	International Business Machines
ICD	International Classification of Diseases
ICI	International Pharmaceutical Industries
IMI	imipramine
IMPS	Inpatient Multi-dimensional Psychiatric Scale
IND	Investigational New Drug
IRB	Institutional Research Board
IQ	intelligence quotient
JAMA	Journal of the American Medical Association
JB 8181	desipramine
K	Kentucky
LA	Louisiana; Los Angeles
LAAM	levacetylmethadol
LICM	Long Island College of Medicine
LSD	lysergic acid diethylamide
LSU	Louisiana State University
KY	Kentucky
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MD	medical doctor
MHPG	3-methoxy-4-hydroxy phenylethylene glycol
MNI	Montreal Neurological Institute
MRC	Medical Research Council
MRI	magnetic resonance imaging
MSCEI	Mayer, Saloway, Caruso Test of Emotional Intelligence
MSRPP	Multi-dimensional Scale for Rating Psychiatric Patients
NA	Narcotics Anonymous
NASA	National Aeronautics and Space Administration
NCEAA	National Collegial Athletic Association
NCDEU	New Clinical Drug Evaluation Units
NDA	New Drug Application
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NMDA	N-methyl-D-aspartic acid
NOSIE	Nurses Observation Scale for Inpatient Evaluation
NP	neuropsychiatry; neuropsychopharmacology

NSF	National Science Foundation
NTIES	National Treatment Improvement Evaluation Study
NYU	New York University
OB/GYN	obstetrics and gynecology
OPRL	Outpatient Psychiatric Research Laboratory
PBI	protein bound iodine
PCP	phencyclidine
PDR	Physicians Desk Reference
PEP	Psychiatric Evaluation Profile
PET	positron emission tomography
PSC	Psychopharmacology Service Center
PSF	Psychopathological Symptom Form
PhD	doctor of philosophy
PI	principal investigator; New York State Psychiatric Institute
PMDD	premenstrual dysthymic disorder
PMS	premenstrual syndrome
PNAS	Proceedings of the National Academy of Sciences
POMS	Profile of Mood States
PR	public relations
PRB	Psychopharmacology Research Branch
PPO	Preferred Provider Organization
PRB	Psychopharmacology Research Branch
PRN	pro re nata (when necessary)
PSC	Psychopharmacology Service Center
PT	personal therapy
PTSD	post-traumatic stress disorder
QTc	QT interval corrected for heart rate
RCT	randomized clinical trial
RDC	Research Diagnostic Criteria
RDRS	Raskin Depression Rating Scale
REF	research on endocrinology and drugs
RFA	request for application
RO1	Research Project Grant Program
RPI	relapse prevention inventory
RU-486	mifepristone
SADS	Schedule for Affective Disorder and Schizophrenia
SADSc	SADS shortened version
SAFTEE	Systematic Assessment for Treatment Emergent Events
SAS	statistical analysis system
SCL-90	Symptom Checklist 90
SKF	Smith Kline & French

SNP	single nucleotide polymorphism
SRAS	Self Rating Anxiety Scale
SRSD	Self Rating Scale for Depression
SRSI	Self Report System Inventory
SSF	Somatic Signs Form
SSRIs	selective serotonin re-uptake inhibitors
TB	tuberculosis
TCA	tricyclic antidepressant
TD	tardive dyskinesia
TEOSS	Treatment of Early Onset Schizophrenia Spectrum Disorders
THC	tetrahydrocannabinol
TN	Tennessee
TNI	Tennessee Neuropsychiatric Institute
TRH	thyrotropin releasing hormone
TV	television
U boat	unterseboot (German)
UCLA	University of California Los Angeles
Conn	University of Connecticut
UK	United Kingdom
UNC	University of Northern Carolina
USC	University of Southern California; University of South Carolina
USAF	United States Air Force
UT	University of Texas
UTMB	University of Texas Medical Branch
V1	Verzeltungswaffe 1 (German)
V2	Verzeltungswaffe 2 (German)
VA	Veterans Administration
VACO	Veterans Administration Central Office
VIP	very important person
VJ Day	Victory over Japan Day
WHO	World Health Organization
WWII	World War II

INTRODUCTION
Jerome Levine

I consider myself fortunate to have been asked by Tom Ban to participate in this ambitious "Oral History of Neuropsychopharmacology" project, by serving as Editor of Volume 4, entitled "Psychopharmacology". As I complete fifty years in psychopharmacology research and research administration, this role has given me the opportunity to "hear" through the words of my colleagues their thoughts on what we have experienced together.

To me, what this volume covers is at the core of what has transpired over the years. Clinical psychopharmacology, by observing and documenting that administration of chemical compounds could markedly improve the symptoms of mental illness stimulated the rapid growth of research. Once that observation was made it drove the field to prove that the changes were real and to understand the mechanisms involved. This necessitated the development of new methodologies, both clinical and basic, and has given rise to the domain we now refer to as neuroscience.

The oral histories in this volume are from investigators identified with the development and application of methods to clinically assess the efficacy and effectiveness of compounds thought to be useful in the treatment of mental illness. Their histories span a period from when proof of efficacy was not required and there were no standardized procedures or guidelines for establishing it, to today, where methods are so standardized that many see these activities as development, not research.

We did not get from there to here in one clear and straight research line. The experiences related by the investigators in this volume present the nuanced ways in which the field moved forward, influenced by institutions and organizations as well as by individuals. Despite the vast increase in our knowledge of how brain and mind function and malfunction, when it comes to evaluating a pharmacologic intervention in mental illness we still depend on the clinical trial, evaluation methods and experience chronicled in this volume.

DRAMATIS PERSONAE
Barry Blackwell

The following pages introduce the dramatis personae of this volume in enough detail to give a framework for understanding their achievements.

Joseph Autry III has been a person of considerable but largely unsung influence on our field. From the start of his career he knew exactly what he wanted to do. His undergraduate majors at Rhodes University in Memphis (a small, private, Presbyterian College) were in chemistry and psychology, two disciplines he anticipated would enable him to treat psychological disorders with medication. His undergraduate work and medical training at the University of Tennessee were supported by a scholarship and two fellowships, one of which, from NIMH, was for research on γ globulins in schizophrenia, while still a medical student.

True to his ambition he completed an internship in medicine (1970) before starting his psychiatric residency in the NIMH model program at St. Elizabeths Hospital during which he won a Falk Fellowship from the APA (1972) and the William Alanson White Award for the best paper by a psychiatric resident (1973).

At age 30, in the two years following graduation, he fulfilled no less than seven different roles. He served as a Lt. Commander in the US Navy and Chief of Psychiatry at the Naval station in Norfolk, Virginia, consultant to a Drug Counseling center, Psychiatrist at a Community Mental Health Center, faculty Instructor at East Virginia Medical School, psychiatrist and consultant to a private practice group and consultant to the NIMH Center for Studies of Schizophrenia.

In 1975 Dr.Autry moved from Norfolk to Washington DC and divided his time between two tracks which have remained constant throughout the next quarter of a century. He set himself up in part-time private practice to create a real life link that would infuse and inform his major role as an administrator and researcher in the extramural programs at the NIMH.

Here he has held a variety of different positions with varying responsibilities. In 1975 he developed the Mental Health Clinical Research Centers Program, encouraging the development of research in depression, anxiety, schizophrenia and severe childhood disorders. After five years, in 1980, he became Chief of the Behavioral Medicine and Psychobiological Processes Section and during this time received the ADAMHA Administrator's Award. In 1982 he became Acting Deputy Director, Division of Extramural Research Programs and two years later, was promoted to Director of the Division. This

included responsibility for development and support of basic research, clinical treatment and applied research.

From 1986 Dr. Autry became Director of the Office of Policy Analysis and Co-ordination, a position that involved planning, legislation and program evaluation. His next move (in 1987) was to take an analogous position at ADAMHA, the parent agency of NIMH.

At the time of this interview (1997) Dr. Autry was mainly involved in developing and evaluating new drug abuse prevention programs in 120 Federal agencies, a task he relished because, "It was one of the few places in the Federal Government where you can actually take research and turn it into policy in a matter of months".

At one point in this interview, Leo Hollister remarks, "God, you've had your hand in a lot of different things". He sounds surprised as others who read the interview and this biography may be unlike almost all the scientists in this and the other volumes Dr. Autry's influence has been through the way his philosophy and administrative skill have shaped our field and facilitated the work of others.

Thomas A. Ban is an iconic figure in psychopharmacology. There is no living psychiatrist with a comparable scientific, conceptual, international and historical grasp of the breadth and depth of our field.

Tom was born in Budapest, Hungary, in 1929, eighty one years ago. This interview was conducted by Leo Hollister in 1996 and is a cogent and inspiring record of Tom's career that spans fifty six years, beginning with his graduation from Semmelweis University as a physician in 1954; the year chlorpromazine began to transform the practice of psychiatry.

Tom's first two years of psychiatric training at the National Psychiatric and Neurological Institute in Budapest were behind the Iron Curtain and ended when an anti-communist uprising in 1956 caused him to leave his native country, first for a brief stay in Vienna and then to Montreal, Canada, at the invitation of Wilder Penfield who learned of Tom's award winning medical student dissertation on post-traumatic epilepsy.

From a foothold as a Fellow at the Montreal Neurological Institute he completed a rotating medical internship before beginning residency at McGill University and Verdun Protestant Hospital where he met Heinz Lehmann on the first day and began research with him on the second. It was a collaboration that would last nineteen years until Heinz Lehman's retirement and Dr. Ban moved on to Vanderbilt University in Tennessee in 1976. The time between Tom's graduation with distinction (1960) and this career transition was filled with accomplishments, detailed in the interview.

This included pioneer work on human conditioning paradigms seeking to link psychopathology with psychopharmacology. Tom then organized and

eventually became Director (1970) of the first Division of Psychopharmacology in any psychiatric department in the world. With Dr. Lehman they developed one of the first Early Clinical Drug Evaluation Units (ECDEU) funded by NIMH and evaluated all the psychotropic drugs in clinical studies from the mid 1960's to the mid 1970's. During this time Tom received five named research awards and authored eleven books on conditioning, psychopharmacology and psychiatric diagnosis. McGill also became part of the International Reference Center for Psychotropic Drugs, organized by the NIMH and the World Health Organization. McGill was the first to train fellows from around the world to become teachers of psychopharmacology in developing countries.

The move to Vanderbilt in 1976 was marked by Dr.Ban's promotion to Full Professor of Psychiatry and Director of Clinical Research at the Tennessee Neuropsychiatric Institute (TNI) and later (1983), Director of the Division of Clinical Psychopharmacology. Early on there is some delightful dialog about the virtues and vicissitudes of writing books stemming from Tom's unusual collaboration with Marc Hollander, Chair of Psychiatry and a psychoanalyst. Their book, *Psychopharmacology in Everyday Practice* (Karger, 1980) was translated into Japanese and Dutch. Discussing this, Leo Hollister comments that compared to writing a book, "You make more money digging ditches". Tom Ban's response is, "Writing a book forces me to conceptualize what we found out in our research and integrate it with the information I read about. That, in itself, I find a rewarding experience". For the record, today Tom is the author, co-author or editor of fifty books and seven hundred articles. He co-edited with Fritz Freyhan and Pierre Pichot the series Modern Problems of Pharmacopsychiatry and the Journal, International Pharmacopsychiatry.

Tom's insightful opinions about the shortcomings of consensual (DSM) diagnosis and the spectrum disorder concept are an important part of the interview and relevant to contemporary research sterility and industry hegemony in drug development. These concerns, incubated at McGill, created the framework for Tom's major research initiatives at Vanderbilt which were devoted to developing methodology to tease apart and define treatment responsive categories. This involved the development of novel diagnostic criteria with sufficient sensitivity for the task.

Dr. Ban is the recipient of several distinctions including the John F. Kennedy Medal of the John F. Kennedy University of Argentina (1991), the Heinz E. Lehmann Research Award of the New York State of Mental Health (1996), and the Paul Hoch Distinguished Service Award of the American College of Neuropsychopharmacology (2003). His diverse interest and international involvement is reflected by his election an Honorary Member of many societies, including the Collegium Internationale Neuro-Psychopharmacologicum, the International Wernicke-Kleist-Leonhard Society, and the Argentine

Association of Biological Psychiatry, The Societe Royale de Medicine Mentale de Belgique, and the Hungarian Psychiatric and Psychopharmacology Associations. He is also President of the International CODE Collegium.

The interview ends with a discussion of Tom's involvement in history; "It is difficult for me to see how research could contribute to the development of a field if it is not done in a historical context". This explains his work in recording the history of both the CINP and the ACNP, and foretells his recent efforts into the early hours of every morning to complete An Oral History of Neuropsychopharmacology in time for the fiftieth anniversary of the ACNP.

Tom is not only the architect but also the builder of this project. He has marshaled over 230 interviews into ten volumes, recruited and ridden herd over editors, designed the format and written a preface to each compilation which clarifies its theme and links each volume to the next.

As his willing collaborator for over two years on several volumes I am able to speak between the lines of this interview. Despite his amazing accomplishments Tom remains a humble, tolerant and modest man, of necessity stubborn and persistent, but with a poet's heart and a mischievous sense of humor.

Barry Blackwell s interview follows the pattern for the series; a modestly structured format for dialog between two scientists (usually psychiatrists) which begins with enquiry about early life and education on the assumption that the child is father to the man. This often leads to an understanding of why medicine and why psychiatry. But not this time; confronted with the story of World War II disruption and childhood in India the interviewer notes, "you certainly had a different type of education" and 'why psychiatry?' is not pursued.

Nobody at Guy's Hospital expected the captain of the oldest rugby club in the world and a beer swilling extravert to opt for psychiatry. It happened this way. Barry began the obstetric rotation in his final year as a student. He was assigned an "elderly primip" who claimed to have no understanding of how she became pregnant; she was terrified of anything entering or leaving the birth canal. Barry asked for a psychiatric consult; the obstetrician declined. Next he suggested a Caesarian section; the obstetrician refused. An intravenous drip was set up to force the patient into labor and Barry sat, holding her hand, while she screamed throughout the delivery. That same week the Lancet published a leading article titled, "Human Relations in Obstetrics" by the Professor of Obstetrics at another teaching hospital. It was a temperate plea for obstetricians and midwives to raise their eyes and attitudes above the umbilicus. Barry wrote a letter to the Editor (May 21, 1960) expressing agreement and outrage. It was published as the first letter in the correspondence section above his name and hospital.

The sequel took place some months later when Barry returned to Cambridge to take his final exams. All went well until the obstetric viva. The examiner greeted him by name and told him to perform a vaginal exam. Struggling to put size seven gloves on his size eight hands the obstetrician commented, “I can see you don’t put gloves on often, Mr.Blackwell”.

A week later Barry discovered the obstetrician had exercised an ancient university right to fail to graduate a student irrespective of overall performance. The penalty was an extra six months of obstetrics before taking the subject again (and passing).

Barry’s path to psychiatry from high school was via the Army (1952-1954), Cambridge University (1954-1957), Guy’s Hospital (1958-1962) and acceptance to the Institute of Psychiatry (Maudsley Hospital) in 1962 during the waning years of Aubrey Lewis’ reign (1962-1967).

At age 28, as a first year psychiatric resident, Barry played a leading role in the discovery and explanation of the interaction between MAO inhibitors , cheese and other amine containing foods including a two year pharmacology fellowship working with rats and cats. In six years as a resident and research fellow at the Maudsley he published twenty scientific articles, nine on the cheese reaction and eleven on other topics and research projects.

In his spare time Barry played rugby, served as a major in a reserve army field ambulance and moonlighted in family practice on weekends, wrote leading articles and annotations (anonymously) for the Lancet, and sired three children.

Premature notoriety is not necessarily the gateway to a successful career. Congenitally clumsy and preferring humans to rats, Barry rejected basic research. A growing reputation and a precocious list of publications didn’t stifle larger doubts about psychiatry itself. Reluctant to give up the breadth of medicine for a narrower specialty he took a time out in suburban family practice but kept one foot inside the research tent. Working as a G.P. he collaborated with a resident colleague, David Goldberg, in the validation of the General Health Questionnaire (GHQ) which David designed and that later became the most widely used instrument to detect potential mental illness in primary care, translated into 38 languages. David went on to become a highly distinguished psychiatrist, successor to Aubrey Lewis, and knighted by the Queen for his service to the profession.

In family practice Barry learned a lot about the milder and earlier forms of mental illness and their response to lower doses of drugs. (Unfairly disparaged, then and now, by “the expert”). Although he missed the hour long, in depth, interviews of psychiatry he came to appreciate that getting to know patients can be a sequential experience over repeated visits. Even the despised 15 minute “med check” can be additive if properly structured. Years

later he published an article in JAMA on "Primary Care Psychiatry" that illustrates this theme. It was translated and became the cover of the journal's Japanese edition!

After a year Barry realized that the driving force to his ambition was curiosity about questions at the interface between medicine and psychiatry. That collecting, analyzing and interpreting data was his natural forte. But this required time to think and plan that would fit better in an academic environment.

America was a natural magnet for his enthusiasm and energy while Industry offered the time and resources to explore the country and learn the culture. The Professor of Psychiatry at Guy's Hospital thought that at age 34 he, "might just make it". The academic climate of psychiatry in America was still strongly psychoanalytic and while Barry enjoyed challenging and disputing its assumptions and dogma he also began to appreciate and assimilate its insight into human behavior, including his own. Becoming more "psychologically minded" had a significant influence on his future interest in patient compliance and illness behavior.

This interview covers the thirty years between arrival in America and retirement (1968-1998) during which Barry was Director of the Psychosomatic Unit at the University of Cincinnati and then the Chair of Psychiatry at two Midwest medical schools; one new and community based (Wright State) and the other established and inner city (University of Wisconsin at Milwaukee). During this time period Barry published almost two hundred scientific articles, book chapters, editorials and commentaries. Thirty of them involved the collection, analysis and publication of clinical material. These included clinical pharmacology studies of side effects, mechanisms of action and placebo responses (Phase 1 studies), traditional Phase II placebo controlled studies, Phase IV (post marketing) studies and surveys, illness behavior treatment, novel educational strategies and patient compliance.

Two factors distinguished these studies. Almost all were designed to provide educational opportunities to a diverse body of students or collaborators and almost none were funded. The design, implementation and interpretation were dependent on the time and talents of the participants and co-authors. These included nurses, medical students, psychologists, pharmacy and pharmacology graduate students, pharmacologists, internists, psychiatric and medical residents, statisticians, a drug company representative, a sociologist, an ethicist, an anthropologist and an English professor.

Towards the end of his career Barry edited two books. One was co-authored with a community and psychoanalytic psychiatrist (Jon Gudeman) and a behavioral psychologist (Len Sperry). Its topic was the art of Case Formulation applied to the DSM framework but intended to expand its descriptive parsimony and procrustean rigidity. The second book, "Treatment

Compliance and the Therapeutic Alliance" reviewed the concept, evolution and manifestations of compliance followed by multiple contributors who offered insights to understand and influence the therapeutic alliance including administrators, psychologists, nurses, pharmacists, psychiatrists, advocates and consumers.

During his career Dr.Blackwell was appointed a Full Professor of Psychiatry, Pharmacology, Applied Behavioral Science and Medicine. He garnered a number of awards including, The Taylor Manor Award for Discoveries in Biological Psychiatry (1970), Medical Student Golden Apple Award (1975), Resident Teacher of the Year (1988 and 1993), NIMH Administrator's Award for Meritorious Service (1991), APA Warren Williams Award (1992), NAMI Exemplary Psychiatrist (1993), Grand Avenue Club (Fountain House) Annual Award (1998), Paul Winchester Spirituality Award (2003), Mental Health Association "Unsung Hero" Award (2004).

In 1998 Barry "took down his shingle" and enrolled in the Catholic Seminary for graduate courses in Philosophy and Religion. After discovering he was "spiritually handicapped" he devoted himself to charitable and part time clinical work, founded a non profit organization, "Faith in Recovery" to connect people with mental illness to faith communities and currently works one day a week as the only psychiatrist in a women's minimum security prison.

For the last two years he has worked closely with Tom Ban to help bring this history project to a conclusion in time for the ACNP fiftieth anniversary in 2011. He has edited two of the ten volumes and written over sixty biographies of the contributors. It has been a labor of love and perhaps a recompense for his long absence from the affairs of the organization.

Charles L. Bowden began his prolific career as an engineering student at the University of Texas in Austin (1957-1960) but halfway towards graduation realized it was, "too much removed from people" so he switched to Baylor College of Medicine in Houston (1960-1964) where he "could combine science with the desire to impact peoples lives". It proved to be a profitable marriage of left and right hemispheres.

At the cusp of neuropsychopharmacology and inspired by charismatic teachers, including two future Nobel Laureates, Charles believed that the future of psychiatry would emulate internal medicine and move away from, "lying on a couch", towards biological treatments. To prepare for this challenge he completed a year of internal medicine (1964) before psychiatric residency at New York State Psychiatric Institute (1965-1968) a program he chose because, "I wanted top training … at a most competitive place".

During residency he worked under Bob Spitzer and Jean Endicott using structured rating scales to measure the outcome of methadone treatment, an

experience he put to good use during his Public Health Service (1968-1970) at the NIMH Clinical Research Center in Lexington, Kentucky. This led to three articles in the American Journal of Psychiatry on long term outcomes of methadone maintenance.

During his time in Lexington he spent a day a week at the University Of Kentucky Department Of Psychiatry where he became familiar with Myron Sandifer's work on the US-UK cross cultural study. The over diagnosis of schizophrenia in America and under recognition of bipolar disorder, combined with his appreciation for the ability of methadone to achieve psychosocial stabilization of a mental disorder, laid the foundation for Dr.Bowden's future seminal work on mood stabilizers.

This interest evolved when he accepted an academic appointment at the University of Texas Health Science Center and became familiar with the NIMH collaborative study on the psychobiology of depression. Looking for a broader research palette his interest switched from narcotic addiction to bipolar disorder. Concerned with how poorly lithium was tolerated and how ineffective it was on the depressive component he responded energetically and creatively to an invitation by Abbott laboratories to study valproate, enlarging their small proposal into a large scale study which contributed to FDA's approval of divalproex in 1995. This also led to co-editing a book on, "*Bipolar Medication; Mechanisms of Action.* (APA Press, 2000).

Dr. Bowden's career trajectory at the University of Texas was rapid and expansive. Six years out of residency (1974) he became the Nancy U Karren Chair of Psychiatry and was appointed Professor of Family Practice in 1978, the year in which he published his book on, *Psychopharmacology for Primary Care Physicians* (Williams and Wilkins, 1978). Three years later he also became Professor of Pharmacology (1981) and in 1986 he was appointed Chief of the Division of Biological Psychiatry.

Dr. Bowden's literary research and administrative accomplishments are prolific. He has authored over 380 scientific articles of which he is principal investigator on 64, funded by the NIMH, Foundations and pharmaceutical companies. His resume lists involvement in 68 task forces and committees in various departments of the medical school and his national and international consultancies include the VA, NIMH, APA, DHSS and ADAMHA.

Most significantly his early commitment to patient care is reflected in active participation in the two largest patient and family advocacy organizations. Since 1993 he has been a member of the Scientific Advisory Board of the National Depression and Manic Depressive Association (NDMDA) and has twice received their awards; the Gerald Klerman Investigator Award (2001) and the Falcone Prize for Outstanding Achievement in Mood Disorder

research (2008). In 2006 Dr.Bowden also received the Mind of America Scientific Research Award from the Alliance for the Mentally Ill (NAMI).

Dr. Bowden is a visiting professor at several Universities, and actively involved in numerous professional societies, notably the APA where he has served on many committees, task forces, expert panels and review boards, including the Executive Committee of Psychiatric Residency Training (1981-1982). He is a Fellow of the ACNP and former member of the Finance Committee and also a member of the CINP. Predictably he is a journal reviewer and member of numerous editorial boards including Associate Editor of *Acta Psychiatrica Scandinavica.*

Jonathan O. Cole is among the handful of true pioneers who lived long enough to be interviewed for this history series. The interview was conducted by Leo Hollister in 1994 when Jonathan was 69 years old, fifteen years before his death at the age of 84 in 2009.

Jonathan was a much beloved member of ACNP, a member of its Founding committee, a Life Fellow Emeritus, an early Council member (1961-1965) and its fifth president (1996). He was genial, unassuming and plain spoken; someone who explained his philosophy as, “it was much easier to get along with people than to enter into a fight with them”.

This interview is precious for three reasons; it is a record of Dr. Cole’s unique contributions to the field, it paints a picture of the earliest organizing events in psychopharmacology and it links the present to the13 past members of the ACNP, 10 of whom died before they could be interviewed but are named in this one. The three exceptions are Sam Gershon (Volume 1), Max Fink (Volumes 2 and 9) and Heinz Lehman (Volume 1).

Jonathan was born in 1925 and attributed his career choice to the fact that his mother had bipolar disorder with a “fixation on a surgeon” (thank goodness that didn’t dictate his choice of specialty) and his best friend in boarding school who had a physician father. He was educated at Harvard (1942-1943) and Cornell University Medical School (1944-1947) during and after World War II. After medical internship at Peter Bent Brigham (1947-1948) he completed psychiatric residency at Payne Whitney Clinic in New York (1948-1951). After graduating he served as an Army psychiatrist at Fort Bragg, running an insulin coma unit and then in Fukuoka, Japan (1951-1953) as Head of the Neuropsychiatric Service.

At a time when reserpine and chlorpromazine were just entering clinical practice the National Academy of Sciences was recruiting psychiatrists leaving the armed services to find someone to staff four committees on stress, psychiatry, drug and alcohol abuse and sexual disorders. (1953-1956). As Jonathan puts it, the committee on psychiatry was, “without a function” since

it was supposed to advise the army on psychiatric research but, “the army didn’t want any advice”.

So he left the National Academy to become Chief of the Psychopharmacology Service Center at NIMH (1956-1966), later Chief of the Psychopharmacology Branch (1967). His first task was to organize a national conference (1956) under a grant to Ralph Gerard which yielded the proceedings for their co-edited book, “*Psychopharmacology: Problems in Evaluation .* (1959).

As Chief of the Psychopharmacology Service Center Jonathan set up a multi-center project comparing three phenothiazines to placebo in nine hospitals (seven were non academic) and later he established the Early Clinical Drug Evaluation Units (ECDEU) which became a national forum for collaboration between industry and investigators. This was a time when grants were awarded on perceived merit without formal bids or RFPs but were sufficiently easy to get that, “nobody complained in those days”.

In 1967 Dr.Cole left the NIMH to become Professor of Psychiatry at Tuft’s Medical School and Superintendant of Boston State Hospital at age 42. By now he had published 15 articles in leading journals mostly on outcome of phenothiazine treatment, collaborating with Gerry Klerman, Karl Rickels, Marty Katz and Bob Prien, among other early investigators. His research attained national recognition with the Hoffheimer Prize from the APA (1969) and he had already been the first recipient of the Paul Hoch Distinguished Service Award (1965) for his significant services to the ACNP.

Dr. Cole’s nine years at Tufts University and Boston State Hospital (1967-1976) were during the era of “deinstitutionalization” and the “revolving door” between state hospitals and their urban communities. Jonathan comments that, “he helped put the hospital out of business” a process about which he had, “acute attacks of guilt, doubt and what not”. Once that task was accomplished he accepted the Chair of Psychiatry at Temple University, “to get out of town” but after only a year he came to dislike Philadelphia and returned to Boston where he took a position at McLean Hospital (1974) and a lectureship in psychiatry at Harvard medical School, eventually (some might say belatedly) becoming a full Professor in 1991.

Much of the rest of the interview provides brief comments on the psychopharmacologists Dr.Cole knew or collaborated with over the next quarter century. That account does not adequately portray the scope of his accomplishments and influence on the field, which are better gleaned from his resume (compiled in 1996).

By the time of this interview Dr. Cole had published over 180 scientific articles, 63 book chapters and 12 books (two for patients and family members) in four major areas, clinical psychopharmacology, drug abuse, geriatric

psychiatry and tardive dyskinesia. Throughout his career he remained a consultant to NIMH. He served on the Editorial Boards of six major journals and served as managing editor for "*Psychopharmacology* for over a quarter century (1960-1986). He was a member of many regional and national hospital, academic and FDA committees. In addition to his career long commitment to the ACNP he was a member of the CINP, the American Association for the Advancement of Science, the APA (Fellow from 1959) and Council member (1974), Secretary (1975-1979) and President (1980) of the American Psychopathological Association.

Jonathan was an excellent and energetic teacher of medical students, psychiatric residents, colleagues and consumers. In 1982 he received the Philip Isenberg Teaching Award from McLean Hospital.

It was not only Jonathan Cole's research, clinical, educational and administrative accomplishments that illuminated the first half century of psychopharmacology but also his temperament which underlay them. Leo Hollister's concluding comment sums that up, "you've always been one of the friendliest and most jovial people in this whole field and it was a delight to talk to you".

Don M. Gallant is a Renaissance man in the several meanings of that term; a person of diverse interests and talents; someone of humanitarian instincts; a role model to remind us of earlier (and perhaps better) times.

From newly graduated physician at age 26 (1955) to the time of this interview at age 72 (2001) the forty six year span of his career began when people with severe and persistent mental illness were incarcerated in asylums, segregated by gender and race, and subjected to insulin coma, ECT without anesthesia and immersion in ice cold water bound by leather restraints.

This biography is based on a 55 page interview by Tom Ban that reads like an adventure story told by a skilled raconteur, backed up by a distinguished curriculum vitae dating from 1997.

Born in Brooklyn in 1929 Don went from Boy's High School to Tulane University where he "fell in love" with physics under the spell of a Department Chair who had worked on the atomic bomb and lost several fingers to radiation. Discouraged by the devastating effects of atomic weapons and seeing no future in bombs Don applied to Tulane Medical School where he was exposed to the charismatic influence of Robert Heath, founding Chairman of the combined program in psychiatry and neurology, a man eulogized by Time Magazine as "the Gregory Peck" of psychiatry. When Don chose psychiatry and to remain at Tulane his best friend accused him of abandoning medicine and refused to speak to him for two days. But Don was prescient enoughto see the writing on the wall; in the summer of his sophomore year (1953) he took a taste of real psychiatry in a summer externship at a New York State hospital. The similarity between psychotic amphetamine addicts and

paranoid schizophrenia convinced him that the illness must have “a molecular or metabolic basis” and that, “psychoanalysis was really off track”.

The attraction to psychiatry was not only intellectual and conceptual but also emotional; “my empathy for patients was very intense”. This affective response infuses the entire interview. Although Don was never in private practice every one of the almost 10,000 patients he saw over 30 years was given a card with his home and office phone number; “they knew they could call anytime they wanted to”. He did what is almost unheard of today, including home visits, seeking information and involvement from relatives and developing support networks to prevent relapses. “The more eyes you have to help you see the world, the more valid the observations become”.

Many themes thread through the interview, illustrated by the anecdotes and information it contains. Predominant among them is a prodigious capacity for hard work, rising at 3.30 each morning to face what often sounds like a seven day work week. Early on, multiple clinical roles included assisting Bob Heath, (who also worked an 18 hour day), in his pioneer and controversial work using subcortical electrodes to locate and identify EEG patterns in schizophrenia. Working with Mel Bishop, and learning statistics from him, Don also became co-principal investigator of one of the first ECDEU programs set up by Jonathan Cole at NIMH. Subjects for the research studies of the earliest psychotropic drugs were recruited from four different patient populations. An outpatient service at Charity Hospital in New Orleans, a schizophrenic research unit at East Louisiana State Hospital (a daily five hour commute over secondary roads), a 32 bed alcohol and drug abuse unit at Southern Louisiana Hospital in Mandeville and New Orleans outpatient Alcoholism Clinic. Research on these diverse populations yielded 35 publications in just three years (1963-1965) and contributed to Don’s acceptance as a member of the ACNP in 1963. Later he became a Council Member (1973-1975) and during this period he was also Chair of the Ethics Committee and spent considerable time developing the ACNP’s first Statement of Ethical Principles. Finally he became a Life Fellow Emeritus.

In what Don calls “spare time” (Friday afternoons and all day Saturday) he set up a free general medical clinic in a low income housing project (the Fischer Project) and introduced an innovative method for early identification and reintegration of school dropouts.

Not only a clinician–researcher Don is a much admired and respected educator. Following a Career Teacher Grant from NIAAA and NIDA (1979-1982) he became Director of Medical Student Education for the Department of Psychiatry (1981-1991) and has continued teaching after becoming Professor Emeritus in 1991. In exchange for an office and secretary he teaches medical students and psychiatric residents “pro bono” three days a week. For twenty

years he received the Tulane medical students annual "Owl" Award and in 1991 he received the Gloria P. Walsh Award from the School of Medicine for, "inspiring teaching, wise counsel and keen interest in the welfare of students".

Don's sense of humor is reflected in several anecdotes and by reading between the lines of his bibliography which includes over 230 citations (including 36 book chapters and 9 books). Tucked away is an article on "*Viewpoints on Coital Positions*" for which the Journal " Medical Aspects of Human Sex" paid for his expertise and another titled, "*A Training experience for the medical student: Gallant s guide for gourmands .*

Those who know Don well believe that his lifelong love affair with New Orleans may be as much about its cuisine as its academic culture. Of course he manages somehow to combine the two; many of the staff members at his favorite culinary venues are former patients. Of the Cajun people he says, "They love to drink and they love to talk, so they are very good patients".

Towards the end of the interview, when Don is asked to name his most important contribution to the field he states, "Probably my main source of pride is having been always available to my patients twenty four hours a day, seven days a week, even though it involved thousands and thousands of patients".

Don Gallant's contributions to psychopharmacology are impressive and innovative just as his opinion of them is modest. But students taught and patients cared for may be a more enduring epitaph than a bibliography.

George Gardos is interviewed by Tom Ban, a fellow Hungarian by birth. Each escaped in the anti-communist uprising in 1956 and both ended up as clinical psychopharmacologists in America but by very different career pathways.

George had just started medical school when forced to leave his native country and completed his training at Bart's Hospital (St.Bartholomew's) in London, England in 1962. He graduated with "practically no exposure to psychiatry" and had never heard of chlorpromazine when asked about it in the oral pharmacology examination. The examiner was unimpressed and perhaps this is why George wrote an editorial almost twenty years later (in the Journal of Clinical Psychiatry) calling for the demise of oral exams in psychiatric Boards!

Unsure of his future George spent a year in Rhodesia (Now Zimbabwe) as assistant to a neurosurgeon. He discovered he was not "cut out" for a surgical career but was encouraged to do clinical research and in 1964, at age 26, published his first article in the Central African Medical Journal on two cases of subdural hemorrhage complicating anti-coagulant treatment.

George then came to America on a student visa to obtain a Master's degree in psychology from Tuft's University with a thesis on the plasticity of the

nervous system in response to deflected auditory stimuli. His visa was on the verge of expiring when he chanced on an opportunity as a research associate at the Massachusetts Mental Health Center working under Al Dimascio and Dick Shader, alongside Carl Salzman and Roger Meyer on early trials of benzodiazepines.

Dr.Gardos soon realized he needed to validate his medical degree in America and began a psychiatric residency at Boston State Hospital where Milton Greenblatt was pioneering community programs to support de-institutionalization prior to the arrival of his successor, Jonathan Cole. After completing residency at Beth Israel Hospital (1969) George returned to Boston State where he remained for eight years, mentored by Jonathon Cole and Seymour Fisher. Dr Cole was a “superb clinician” and Boston State an “exciting place” where George worked on the dose-effect relationship of early neuroleptics and also on social adjustment and family care of discharged patients.

When Dr.Cole moved to McLean Hospital George joined him part time and became involved in the major research enterprise of his career as the Principal Investigator on the long term (15 year) follow up of 200 patients with tardive dyskinesia. A third of Dr.Gardos’ 44 original reports and two thirds of over 110 publications are on various aspects of this disorder including its measurement, etiology, natural history, treatment and long term outcome. He is the first author on the majority of these publications, the co-editor of two books on the topic (APA Press, 1984 and 1986) and Consultant to the APA Task Force on Tardive Dyskinesia (1978-1979).

Dr.Gardos is a member of both the CINP and ACNP and served as a member of the ACNP Education and Training Committee (1989-1992) and the Ethics Committee (1995-1998). He has been an Associate Clinical Professor at Harvard Medical School since 1994.

George considers himself a “dinosaur” because, for him, science is rooted in clinical care and the patients he has followed in his research and private practice for thirty years or more.

Burton J. Goldstein s path to clinical psychopharmacology is interesting and unusual, a surprise even to himself. His original career choice was pharmacy and he graduated with a bachelor’s degree from the University of Maryland in 1953, obtaining his best grades in pharmacology.

During the Korean War, infantry and officer training broadened his horizons and ambitions so after returning to civilian life he was accepted by his alma mater into medical school (1956-1960). He paid his own tuition via the G.I. Bill and seventy hours a week of summer work in a pharmacy.

After graduating he made the only major relocation of his life, entering internship and psychiatric residency at Jackson Memorial Hospital in Miami

where he received an NIMH Training Fellowship (1961-1964). Research was expected but difficult in a county hospital overwhelmed by the clinical demands of serving an indigent population, flooded with recent Cuban immigrants. Nevertheless he published his first paper while chief resident on the prophylactic use of benztropine in extrapyramidal symptoms, (1964). He was rewarded by the offer of a junior faculty appointment at the ten year old University of Miami in a department of Psychiatry with only four full time faculty.

Burt has remained there for his entire career until (and beyond) this interview in 2001, at the age of 71. The accomplishments it details led to becoming Full Professor of Psychiatry in 1973, only nine years after residency. Dr.Goldstein is also Professor of Pharmacology and Professor of Epidemiology and Public Health. From 1972 till 1983 he served as Vice Chairman of the Department and throughout his career he filled a remarkable number, (over thirty), departmental and medical school administrative and clinical assignments.

For a quarter century (1968-1993) Dr.Goldstein was Chief of the Division of Pharmacology and this interview details his accomplishments. Early on this involved the first controlled studies of haloperidol which led to FDA approval and to collaboration with Dean Clyde, whose mood scale they translated into Spanish for use in the Cuban population. Influenced by Karl Rickels and John Overall's work in Philadelphia, on the demographic and socio-economic factors that influence drug response in different populations, Burt began, in 1968, to recruit and study "symptomatic volunteers" for drug studies via advertising. "If I look back on my career that's probably the greatest contribution I made, because it certainly facilitated drug development and drug discovery".

In the 1970's and 1980's Dr.Goldstein's interests shifted to addiction research, beginning locally with studies on the extent to which underlying depression might lead to self treatment with heroin in a methadone population. This led to involvement with the U.S Department of Education and their national attempt to reduce substance abuse in schools. Over ten years (1979-1987) Dr.Goldstein was Principal Investigator on this project in Region IV, supported by successive grants totaling 4 million dollars.

In the later stages of his career Burt has become involved in the interdepartmental Health Sciences Research Center funded by NIDA, headed by the Chairman of Epidemiology and involved in research on the large population of chronic drug users in South Florida.

Dr.Goldstein has had a distinguished career as an educator and mentor of psychiatric residents and clinical faculty, as a member of numerous editorial boards and an active participant in local and national medical societies

and associations, including the ACNP of which he is a Life Fellow Emeritus and member since 1967.

Nationally known and respected as a pioneer in the field of psychopharmacology Dr. Goldstein is also a "homebody", modest about his contributions, who has clung to his roots in Miami for almost a half century where he and Linda raised six children; the "Brady Bunch".

Gerard E. Hogarty, known to colleagues, friends and family as "Jerry" was sufficiently unusual in his career path and accomplishments to be justly considered unique. Like most pioneers in psychopharmacology he was born in the third decade of the twentieth century (1935) and reached adulthood coincident with the advent of chlorpromazine in the treatment of schizophrenia (1954). Everything else was unusual.

The middle child in a Boston Catholic Family, he aspired to priesthood and attended a Jesuit seminary but gave up Holy orders for undergraduate studies in philosophy at Catholic University in Washington DC, followed by a Master's degree in Social work. (1960). Jerry was clearly more a man of fact than faith.

One of the few members of the ACNP without a doctoral degree, when many now have two, (a PhD and M.D.), Jerry preferred to be known by the quality of his work rather than his credentials. With modesty, honesty and humor his curriculum vitae notes his post graduate education consists of, "privately acquired knowledge in biostatistics, psychiatric epidemiology and the conduct of clinical pharmacology trials".

How this happened was also unusual. Trained in conventional psychoanalytic principals of social work with its belief that medications were "symptom covers" for people who needed to be "weaned from oral dependencies" Jerry recognized another religion when he saw it and began work in a Public Welfare Agency. Here he chanced to hear that NIMH was initiating a nine hospital study of chlorpromazine in schizophrenia directed by Jonathon Cole and co-ordinated by Bob Prien. The project needed a social worker to collect and collate patient histories and background. As Jerry states in this interview, "Nobody had ever hired a social worker in that role".

At Springfield State Hospital the Superintendant greeted him with the opinion that social workers had, "Soft heads and big hearts", attributes he set out to remedy by assigning Jerry to work in an admissions office that processed 10,000 patients a year into 3000 beds. He was closely supervised by two psychiatrists, refugees from Nazi Germany; Martin Gross, a disciple of Emil Kraepelin and Arthur Mandel, a pupil under Sakel, the originator of insulin coma therapy, in Vienna. After a year Jerry says he, "Thought like a European".

The nine hospital project led to a second seven hospital study using higher, sometimes toxic dosages, by which time his intelligence and skill were sufficiently recognized to result in a year at the NIMH Psychopharmacology Center (1966) where he learned study design and statistical analysis as well as lifelong relationships with early leaders in the field, including Nina Schooler, Sol Goldberg, Marty Katz and others. With this background, knowledge and training he now knew enough about schizophrenia, what needed to be done, and how to proceed.

Schizophrenia is a cruel disease, striking in time to disrupt the early adult tasks of emancipation, higher education, career development and social affiliation, leading to a life partner. Jerry also knew that while medication rescued those who suffered its ravages from asylums it did little to equip them to overcome the stigma, discrimination, neglect and hostility in the communities or families to which they returned.

Jerry Hogarty's early research recognized and appreciated the immediate and longer term benefits of medication but also the dangers of over dosage and side effects that contributed to poor compliance and relapse. He always referred to the methods he developed to repair the medical and psychosocial shortcomings of contemporary drugs as "add ons".

In the late 1960's, after leaving NIMH, he became Principal Investigator on the first (and still the largest) "aftercare" project; an NIMH funded, placebo controlled study, of 374 newly discharged patients with schizophrenia, followed for two years. This compared chlorpromazine and placebo with a combination of social casework and vocational rehabilitation, alone and combined. Jerry named this earliest psychosocial intervention, Major Role Therapy or MRT.

The remainder of the interview tells the story of how this beginning evolved into three decades of carefully planned incremental research at the University of Pittsburg (from 1974) where Jerry Hogarty developed an international reputation for innovative psychosocial treatments in schizophrenia and earned the title of Emeritus Professor of Psychiatry.

The evolution of this body of knowledge reflects Jerry's persona and skill set. His wife of 20 years, a psychiatric nurse, nicknamed him "Curious George" because of an intense curiosity, a person who valued experience over possessions and an innovative researcher who built progressively on the findings of one study to design the next. His colleagues note that he possessed both clinical acumen and compassion for patients, a talent for meticulous but atheoretical science and an ability to explain complex phenomena in understandable and engaging ways.

Although Major Role Therapy (MRT) was successful overall, there were individual differences in outcome that demanded exploration. Elaborating on

the concept of "expressed emotion" Jerry developed the technique of family "psychoeducation" which trained family members to "cool" the domestic climate by reducing criticism or hostility and increasing warmth and encouragement. He presented this as a "survival guide".

Also important, but somewhat less successful, was Social Skills Training to help patients identify and modify behaviors that "drove family members up the wall". This strategy was refined by devising "a psychological autopsy of relapse", leading to recognition that patients often displayed affective cues before developing cognitive or psychotic features. These early signs were triggered by subtle developmental lags in socialization and communication. This was addressed by a combination of social skills training and developmental tutoring named Personal Therapy (PT), avoiding the term "psychotherapy".

The most recent step in Jerry Hogarty's evolutionary understanding of schizophrenia and its treatment was the recognition that failure to benefit from medication might be contributed to by disease induced delays in social cognitive development leading to a form of pre-adolescent egocentricity that blocks recognition of normal cues and the rules of everyday social interactions. This is dealt with using a small group approach called Cognitive Enhancement Therapy (CET).

Jerry has not been a prolific writer or self publicist; his wife notes, "He didn't need a lot of recognition". Contributing to this is a concern for accuracy and scientific certainty. Much of his research appears in the *Archives of General Psychiatry,* testament to its quality.

Jerry's psychosocial treatment strategies are the subject of three books. *Schizophrenia and the Family: A Practitioner s Guide to Psychoeducation and Management* (Guilford, 1986); *Personal Therapy for Schizophrenia and Related Disorders; A Guide to Individual Treatment* (Guilford, 2002); and *The Cognitive Enhancement Therapy Treatment Manual* (CET Associates, 2005).

Jerry Hogarty has received two of the nation's most prestigious awards for his body of work. The *Stanley Dean Award* (1988) from the American College of Psychiatrists and the *Alexander Gralnick Award (2006)* from the American Psychiatric Association which was awarded posthumously after his tragic death from lung cancer at the age of 71, just over a year after this interview (December, 2004).

Later on in the interview Jerry Hogarty expresses disappointment over the failure of the field to implement the innovative and effective interventions he designed to augment the drug treatment of schizophrenia. "With every progressive psychosocial treatment with increased efficacy that comes closer and closer to the presumed psychophysiology of these disorders, the interest in the field to implement the new treatment has gone down".

He is puzzled and tentative about attributing a cause but speculates on residual therapeutic nihilism towards schizophrenia, reluctance of managed care companies to authorize evidence based treatments, the focus of contemporary basic research on targeting molecules that might enhance cognition and the cost of modern drugs absorbing available resources.

Even this depressing litany doesn't stifle Jerry's innate enthusiasm when he quotes Gerry Klerman's aphorism, "the market place will determine its value". Perhaps this thought and Jerry's wry sense of humor led to choosing a purple cover for his 2002 book as a metaphor at a time when one pharmaceutical company spent billions of dollars advertizing "the purple pill" for a relatively mild medical condition.

Jerry was a man working between two ideologies, seeking to unite them with a biopsychosocial approach, but in a way never fully appreciated by the extremes. "I kind of wandered into this field, completely unprepared, with an antagonistic background in training that I had to overcome". Later, after he defined Cognitive Enhancement Therapy; "I had to beat back a lot of people, the behaviorists, the neuropsychologists, nobody liked it".

Jerry Hogarty joined the ACNP in 1982 in mid career, at the age of 47.

John M. Kane inherited his physician father's zeal for medicine and intellectual curiosity, majored in English at Cornell University and, as a medical student and bibliophile, picked up a copy of Klein and Davis' "*Psychiatric Diagnosis and Treatment*" (1969) in the NYU Medical School library. He still has the original annotated and underlined copy which inspired him to choose psychiatry as a career and Hillside Hospital as the place to do psychiatric residency (1971-1974). There he was mentored by Don Klein in clinical practice and research methodology. John supplemented his psychiatric training at Columbia University with graduate courses in anthropology, sociology and psychology.

His research career began immediately after graduation and a year later (1976) he became Director of Psychopharmacology Research at Hillside and published his first scientific article in the American Journal of Psychiatry on Tardive Dyskinesia. Since then John's career has been remarkably stable, focused and productive throughout the thirty nine years he has remained at Hillside (1971-2010) where he became Chairman of Psychiatry in 1988 and Full Professor at Albert Einstein College of Medicine a year later.

The interview tracks his research interests in bipolar disorder, schizophrenia, tardive dyskinesia and clozapine. In less than twenty years Dr.Kane was a Principal Investigator on fourteen different projects funded by NIMH for a total of over fifteen million dollars (1976-1996). This has produced over 200 articles, thirty book chapters and five books. They range beyond the medical aspects of treatment to reflect his earlier training in anthropology, sociology

and psychology. As detailed in the interview he has delved into the prodromal symptoms of schizophrenia, the social and environmental factors that delay onset of treatment, the impact of involuntary treatment, the role of the placebo response in research design and the inadequacy of rating scales to "capture the extraordinary array of domains" of dysfunction in schizophrenia which may require both psychosocial and pharmacological treatment.

It is hardly surprising that John Kane's body of work has exerted widespread influence and attracted well deserved recognition in the field. He has served on numerous NIMH and FDA task forces, review or advisory committees and as a reviewer or editorial board member on fourteen journals. Throughout his career he has been active in the APA and the ACNP. He is a Fellow of the ACNP and member since 1982 serving on several committees, liaison and task forces including public concerns, research settings, schizophrenia, advocacy groups, education and training and, most recently, governmental agencies and industry. (2010-2012).

John has been in wide demand as a lecturer and grand rounds speaker including 28 of America's medical schools and several international venues including, Britain, Mexico, China and Malaysia. Finally, Dr.Kane's research received an NIMH Merit Award (1989) and six national awards, most recently the Heinz Lehmann Research Award (1993).

Martin M. Katz, born in 1927, was a mature young scientist with an undergraduate degree in chemistry and a doctoral degree in psychology from the University of Texas (1955) when psychopharmacology was at ground zero. In this interview (1995) by his peer, Jean Endicott, we obtain a unique "bird's eye" view of the evolution of our discipline that includes an inventory of its triumphs and tribulations over half a century later.

After two serendipitous meetings with Jonathan Cole Marty was recruited to become Executive Secretary of the first Psychopharmacology Advisory Committee at the NIH in support of the Psychopharmacology Research Center (PSC), funded by Congress to develop the new field. This was a multidisciplinary body, chaired by a neurophysiologist and included pioneers who were psychologists, pharmacologists, biologists and psychiatric clinical researchers.

Dr.Katz began by reviewing and supporting novel research programs and after two years reverted to an active research role developing the eponymous Katz Adjustment Scales for measuring clinical and social adjustment and, in 1965, helping to organize the first large national conference on the Classification of Mental Disorders. This led later to co-editing the book, *The Role and Methodology of Classification in Psychiatry and Psychopathology"* (1968),. The following year he co-authored, *The First Year Out; Mental Patients in Transition* (1969), an early account of deinstitutionalization.

Over the next five years (1963-1968) Marty developed a laboratory at NIMH to study what he calls the "bad" psychedelic drugs; a class of compounds he feels was prematurely shelved for political reasons and which might be productively resurrected. During this time he developed an interest in the influence of culture on the clinical manifestations of schizophrenia and wrote a book on the topic, *Characterizing the Differences in Psychopathology among Japanese, Filipino, and Hawaiian Schizophrenics* (1966). In 1968 he pursued this interest at the University of Hawaii before he was invited back to Washington to become Director of the new Clinical Research Branch at the NIMH. Its mission was to stimulate the field with conferences and by supporting collaborative research in five areas, depression, schizophrenia, psychosocial treatments, psychopathology and biological factors in mental illness. Over a ten year span (1968-1978) the budget to accomplish this quintupled from five to twenty five million dollars.

Early on, a key event was the Williamsburg Conference (1969), which highlighted the neurochemical theories of etiology in depression and identified the key areas for development; better diagnosis and nosology, the genetic basis for disorders and ways of testing biochemical hypotheses. The conference and subsequent developments led to two books co-edited by Dr. Katz, *Recent Developments in the Psychobiology of Depressive Illness* (1972) and, *The Psychology of Depression: Contemporary Theory and Research* (1974).

One outcome of the collaborative approach that evolved during Marty's tenure was a seedbed for training a cadre of early outstanding researchers named in the interview. He attributes much of that success to two outstanding leaders, Gerry Klerman in the clinical arena and Jim Maas for the biological effort. A third leg to the collaborative ideal was the Clinical Research Center concept which provided sufficient sustained support to develop programs and scientists. At the conclusion of his tenure as Director of Clinical Research Marty received the Administrator's Award for Meritorious Service from ADAMHA (1979).

After leaving the NIMH and leading up to this interview (1984- 2004), Dr.Katz held a number of appointments at Albert Einstein College of Medicine and Montefiore Medical Center including Director of Clinical and Experimental Psychopathology (1986-1993) and Professor and the first Chief of the Division of Psychology in the Department of Psychiatry (1984-1994). During this time he was the Principal Investigator for NIMH funded research on the Psychobiology of Depression and co-edited two further books, *The Measurement of Depression* (1987) and *Contemporary Approaches to Psychological Assessment ,* (1989). At the time of the interview he was clinical Professor in the Department of Psychiatry.

Currently (2004-) Dr.Katz is Adjunct Professor of Psychiatry at the University of Texas Health Sciences Center in San Antonio. He now has a lifetime body of work that includes over 120 scientific articles and book chapters. Among his latest innovative work is the Video Behavior Evaluation Scales (VIBES). For almost thirty years (1970-1998) Marty served as a Consultant and Advisor to the World Health Organization on a variety of subjects and for ten years (1980-1990) he was Co-Director of the WHO Field Research Center in Hawaii.

Towards the end of this interview, with hindsight, Marty identifies three areas where the exciting discoveries of the first twenty five years (1955-1980) were expected to fulfill hopes for the next quarter century (1980-2005). The first was that new "breakthrough" drugs would no longer be discovered by serendipity or accident but by designing new molecules faster and more effectively, based on biochemical knowledge. But since the introduction of fluoxetine in the early 1980's "nothing really remarkable" has appeared.

Secondly, that the biological basis of psychiatric disorders would be revealed; a simple blood test at the first interview would provide the diagnosis. This too has been a disappointment, "we have yet to find a biological marker for any mental disorder".

Thirdly, that the mechanism underlying the action of drugs would be known, but "that too, is still clouded".

Late in the interview Dr.Katz tries hard to uncover a contemporary silver lining; instead he identifies a shortcoming that may account for the lack of progress. He wonders if our excitement with molecular biology and neuroimaging has led to the neglect of a better understanding of behavior. "If we go to the trouble to get down to such refined, intricate biological measurements, we should be doing the same kind of thing in the sphere of behavior".

The fact that this interview was conducted fifteen years ago hardly modifies its contemporary relevance. Its insights are from a man who was there from the very beginning, a member of the ACNP from 1963, Council Member (1972-1974), Vice president (1978) and now Life Fellow Emeritus. Dr.Katz is also the editor of Volume 10 in this series, devoted to the history of the Organization.

Donald F. Klein is among the pioneers whose medical career began before psychopharmacology was a discipline. Born in 1928 he started psychiatric training at Creedmoor Hospital in 1953 at age 25, responsible for 300 patients in a 6000 bed locked hospital when the only available drugs were paraldehyde and barbiturates.

Don's childhood interest in science was kindled by "fooling with chemistry sets" and visits with his father to the New York Museum of Natural History. He was also intellectually precocious, entering college at 15 and graduating

Magna Cum Laude at the top of his class in 1947, aged 19. Along the way he stumbled across Freud's books in the college library which contained, "all the things I was interested in; mostly sex".

An early ambition to become a research psychoanalyst was extinguished after he exhausted two training analysts at the New York Psychoanalytic Institute. Experience and curiosity must have taught him he was a man of science and reason, not faith. His time in the USPHS at Lexington (1954-1956), where he was mentored by Abe Wikler, "the smartest man I ever met", and work with Max Fink, "a diagnostic nihilist" at Hillside Hospital (1959-1970) asserted their influence and he settled into a career in psychopharmacology.

In 1961 he became an NIMH career investigator (1961-1964), and then Director of Research at Hillside (1965-1970), and finally Director of Research and Evaluation coupled with a full professorship of Psychiatry at the State University of NY, College of Medicine (1972-1976). In 1976 he was appointed Director of Psychiatric Research and Director of the Department of Therapeutics, positions he held at the time of this interview (1994) and subsequently.

Don has produced a prodigious volume of research and numerous textbooks during the half century of his career and he remains a research psychiatrist at NYU from whom he received his Honorary Doctorate of Science in 1998. The Google Advanced Scholar internet site lists three hundred publications dating from 1964, many in the prestigious Archives of General Psychiatry. The most frequently cited (659 times) is, "Diagnosis and Treatment of Psychiatric Disorders", published in the British Journal of Psychiatry in 1970.

Dr.Klein's body of work includes several major areas of interest detailed both in this interview, by Leo Hollister and a later one in Volume 9 with John Davis (with whom he co-authored one of the first texts in the field). They include original and sustained research on the discovery, diagnosis, neurophysiology and treatment of panic disorder and agoraphobia, including its linkage to childhood separation anxiety, the strategy of "pharmacological dissection" and earlier work on MAO Inhibitors and "atypical depression", psychostimulants and tricyclic antidepressants.

This work is the product of over 40 years of sustained support from NIMH as a Principal Investigator (1964-2006), a vindication of the virtue of research center grants of the kind discussed in the interview and which Dr. Klein believes the ACNP should advocate for with heads of Federal agencies. Testimonies to its value are the many awards received by Don over 40 years, beginning in 1964. They include the Society of Biological Psychiatry Gold Medal Award (1990), the Heinz Lehmann Research Award (1991), The

Castello del Pino Award (1990) and the ADAA Lifetime Achievement Award (2005).

Don's contribution to his academic Associations and Societies is equally impressive. He became a member of the ACNP in 1965 and is now a Life fellow. He has served on many task forces and committees, the council, and was President (1981) before receiving the Paul Hoch Award for Distinguished Service in 1991. He has also served as the President of the American Psychopathological Association (1979-1980), the Psychiatric Research Society (1980), the American Society of Clinical Psychopharmacology (1992-1996), and the National Foundation for Depressive Illness (1983).

Dr. Klein has been a consultant to the NIMH, NIAAA, VA, NIH, FDA and APA as well as an editorial board member of many leading psychiatric, research and psychopharmacology journals.

The Anxiety Disorders Association of America honored Don by initiating an Annual Donald F. Klein Early Career Development Award given in his name to a promising young researcher. In doing so they recognized Don as someone who "Revolutionized psychiatric thinking".

James C. Klett was born in 1926 and raised in Jamestown, North Dakota where he attended College intending to major in mathematics, was inspired to switch to psychology, but managed to combine the two in graduate school at UW Seattle where he came under the influence of mentors who were quantitative psychologists and shaped his career interests in statistics and clinical outcomes.

Like many of his medical contemporaries there were not yet any psychotropic drugs when he became a VA trainee in Seattle (1952-1956). Instead he was involved in a clinical trial of pre-frontal lobotomy doing pre and post surgery evaluations.

In 1958 he was recruited to join the VA's Central Neuropsychiatric Research Laboratory (CNPRL) at Perry Point, Maryland where he would remain until his retirement thirty years later (1988). During that time span he became Chief of the CNPRL (1962-1975) and then Chief of the Co-operative Studies program Co-coordinating Center (1973-1988).

The VA had a major role in the earliest multi-center clinical trials and Dr.Klett organized their first comparative double blind controlled study of major tranquilizers, even before the NIMH and State Hospitals eventually did likewise. At that time "there wasn't a single book on how to do a controlled or multi-center study". The interviewer, Leo Hollister was among the psychiatrists involved and they were co-authors when the study was published in the *American Journal of Psychiatry* (1960).

In the first decade of his tenure (1958-1968) Jim was involved in the development of research methodology and measuring instruments including,

the Edward's personal preference schedule (1957), Barron's ego-strength scale (1957), Sequential analysis for rapid screening of new drugs (1959), a patient progress scale (1961), the Inpatient Multidimensional Psychiatric Scale (IMPS) with Maurice Lorr (1963) and the Nurses Observational Scale for Inpatient Evaluations (NOSIE) with Honingfeld.

During the next two decades (1968-1988) Jim's interest expanded into drug and alcohol addiction. His studies with Sam Kain on alcohol withdrawal (1969-1973) are considered some of the leading articles in the field during the last quarter century. Dr.Klett's work on maintenance medications for heroin addicts became instrumental in FDA approval.

In addition to Jim's innovative research he also played key administrative roles. He edited the proceedings of three Annual research conferences on Chemotherapy in Psychiatry for the VA (1959-1961) and eight consecutive conferences for the VA Co-operative Studies in Psychiatry (1968-1975). Throughout his career he served on review committees for the NIMH, FDA, NAS-NRC, NIAAA, VA and NIDA as well as a consultant to WHO, NIH and the SSA. He notes he worked "on one committee or another for 20 years".

When Dr.Klett retired from the VA in 1988 he was awarded the Administrator's Exceptional Service Award. He is a founding member of the ACNP (1961), now Fellow Emeritus and has served on several committees over the years, including Liaison with Government and Industry and Ethics. Towards the end of the interview there is interesting dialog and regret about the diminished roles of statisticians in the ACNP and of independent, well trained clinicians in new drug evaluation studies, "you don't have a wise sensitive clinician who talks to patients".

James H. Kocsis could be considered a "second generation" clinical psychopharmacologist. Born in 1942, his education was interrupted by the Korean War and he did not complete his psychiatric residency at the Payne Whitney Clinic until 1975 at age 33. He became a member (now a fellow) of the ACNP in 1987.

His career includes original and innovative research on what, until then, had been a neglected area; the etiology, nosology, natural history and treatment of what became known in DSM III (1980) as "Depressive Dysthymia". Why Jim became involved and how he has influenced the field are the main topics of this interview, conducted in 2005.

He describes himself as a "melancholic person" whose maternal grandfather suffered from recurrent major depression, treated with ECT. Conviction about the biological nature of depression also came from experiences as an intern at Cornell Medical Center (1968-1969) and a general medical officer in the Navy (1970-1972). As a primary care physician he, "learned a lot about general medicine and about depression". Patients with physical complaints

and illnesses he saw for fifteen minute visits, “got a lot better … on a tricyclic”. At his naval station he became known as “Dr. Elavil”.

Dr.Kocsis’ research career began as a Chief Resident in psychiatry (1975) under the mentorship of Peter Stokes, with whom he published his first paper (on lithium dosage in Mania) in the Archives of General Psychiatry (1976). After residency he began his career as a junior investigator and Assistant Professor at Cornell University (1977), moving up the academic ladder to become Full Professor in 1992.

Jim’s interests were shaped in the 1970’s by the work of Don Klein in what was originally considered “characterologic” or “atypical” depression before being renamed “dysthymia” by Hagop Akiskal. In 1980 the disorder was officially recognized as an Axis I (not Axis II) condition, “largely a political decision” made by a committee that included biological advocates such a Klerman, Akiskal and Klein.

Jim’s research in this arena has followed a logical progression laid out in the interview and supported initially by two major NIMH grants; one as an Associate P.I. with Stokes funded for 16 years (1975-1991) and the other as P.I. for 12 years (1985-1997). Over a span of twenty years the research began with the first, placebo controlled, trials of antidepressants in dysthymia, followed by a long term maintenance study, leading to work on treatment refractory depression and the two thirds of patients who failed to achieve a full remission. Closer examination of this population led to a recognition of the role of life trauma and abuse in etiology and the value of a specific form of cognitive behavioral therapy; Cognitive Behavioral Analysis Systems of Psychotherapy, (CBASP, developed by James McCullough). This body of research is represented by over 100 publications, 20 book chapters and a book, *Diagnosis and Treatment of Chronic Depression* , co-authored with Don Klein (Guilford Press, 1995).

While research has been the main thrust of Dr.Kocsis’ career he has been active in teaching psychiatric residents, medical students and (earlier on) primary care physicians. He has served as a consultant and committee member to the APA (on DSM III-R and DSM IV), NIMH, NCDEU and ADAMHA and also a reviewer on a number of journals.

The interview includes an interesting discussion of the “complex change in the landscape of clinical psychopharmacology over the last twenty five years”. Jim is generous in granting credit to the pharmaceutical industry for developing new compounds and financing research. Concern about dwindling federal grants is reflected in his own support. Since 1991 five out of six most recent grants have been from three different drug companies. He acknowledges that, “sometimes you feel you are being pushed around by people in marketing” and he has been frustrated by, “not being able to get

negative studies published". He believes there should be a specific journal for negative results.

Similar ambivalence about contemporary relationships between industry and research clinicians is reflected by other ACNP pioneers in Volume 9 of this series.

The diversion of Federal support from clinical research to basic science must be especially hard on a psychopharmacologist who volunteered to work in a State Hospital as an undergraduate, entered medical school with a preternatural commitment to a career in psychiatric research , who says, "research always excited me" and who plans to continue doing it , "till I'm about eighty".

Yves Lecrubier was born in Algeria, educated in Spain and France and died in June, 2010, at age 66 in Paris. His interview for ACNP was in 2003, when he was President of the European College of Neuropsychopharmacology, ECNP, (2002-2004).

As a child Yves was fascinated about how the brain might function and in 1964 he began his medical education determined to find the answer, leading to postgraduate training in both psychiatry and psychopharmacology. Eventually he became Director of Research at the world renowned Saltpetriere Hospital in Paris where Charcot welcomed Freud in the late nineteenth century.

Yves was a creative thinker and prolific worker with a wide range of interests that attracted international notice early in his career. His first work was on the nosology of depression where he made an important distinction between mood (which he considered secondary) and energy, where he felt retardation was a key biological feature. As discussed in the interview he moved on to become interested in the contextual, cultural and age related expressions of symptoms in mood disorders.

In addition to theoretical questions he was involved in practical problems of assessment and treatment, developing a 15 minute interview (MINI) that was translated into 45 languages. He was a contributor to the WHO international study of psychological problems in primary care involving 15 countries and over 26,000 patients followed for a year, published in the Archives of General Psychiatry (1993).

Dr. Lecrubier's lifetime body of work included almost 100 scientific articles and several books the most recent of which was, *Progress in Dopamine Research in Schizophrenia* (2004). Some idea of the diversity of his interests can be garnered from the articles he published in the years leading up to his death. Topics included, *False Beliefs in the Treatment of Depression; Guidelines for the Treatment of Anxiety, PTSD and OCD; Anxiety and Impulsivity in Adolescence; Positive and Negative Symptoms in Schizophrenia; PTSD in*

Primary Care and Diagnosis and Classification in Psychiatry. (He was a contributor to DSM-IV –TR).

Dr.Lecrubier's obituary on the ECNP website notes, "His charming personality, creative mind and enthusiastic energy" as well as world wide recognition of his contributions to our field.

At the end of the interview, asked to comment on key changes facing psychopharmacology, Yves pinpoints today's lack of clinical research. He notes we have "an enormous amount of data" in neuroscience and molecular genetics but inadequate classification and measuring instruments to give it meaning and an over reliance on computers. "We should progress in disentangling the groups of patients into relevant targets for research". Had he lived longer he would certainly have contributed to this endeavor.

Jerome Levine, "Jerry" to the many who know him well, played a central role in the early development of psychopharmacology in the United States, the link person between NIMH and an entire first generation of clinical investigators. This interview, by Sam Gershon a fellow pioneer in the field, was recorded in 1955, a year after Jerry completed a twenty year stint at the NIMH, first as a research psychiatrist (1964-1965), then Assistant Chief of the Psychopharmacology Research Branch (1996-1997) and finally as Chief of the Pharmacologic and Somatic Treatments Research Branch (1967-1984) during which time he ran the 18 Early Clinical Drug Development Units, (ECDEU), which were the cornerstone of clinical research, independent of the pharmaceutical industry, and the seed bed for development of standardized procedures and rating scales still in use by investigators and industry today.

Jerry graduated Cum Laude in Chemistry in 1954 and obtained his M.D. with Thesis Honors in 1958, both from Buffalo University. After he completed his psychiatric residency at E.J Memorial Hospital in Buffalo and St.Elizabeth's Hospital in Washington D.C. he served his military draft at the U.S. Public Health Service Hospital in Lexington where he met and was recruited by Jonathan Cole, becoming his Deputy and succeeding him when Jonathan moved to Boston, (1967).

During Jerry's tenure as Chief of extramural research in psychopharmacology he administered a federal budget of $10-17 million with 25 full time employees, distributing close to a million dollars annually in grants and contracts to nationally and internationally renowned researchers. As noted in the interview he engendered a sense of collegiality and continuity in the developing field. In the early years he also participated actively in the design and implementation of studies and later on was also Research Professor at the Maryland Psychiatric Research Center (1985- 1994). In 1997-1998 he took a sabbatical as Visiting Professor at the University of Pisa to set up a Center

for Clinical Pharmacology Data Documentation and organized teaching workshops attended by over 150 academic and industry scientists.

The interview describes Jerry's role not only in the development of promising new drugs but in defining the limits and shortcomings of LSD in the early years and hyperbaric oxygen later on.

In addition to research, teaching and administration Jerry played important advisory and liaison roles to the FDA, WHO, Government agencies, the US Pharmacopeia and Pharmaceutical companies. He became a member of the ACNP in 1972 and is a Life Fellow Emeritus, serving on several committees and as a Section Editor for the publication, *Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines* (1991-1994). He is the Editor of Volume 4 in the historical series in which his own interview appears.

Jerry also served as Vice president and Chair of the Membership Committee of CINP and is the recipient of the APA Hofheimer Research Prize (1970).

There is probably nobody who has a broader view of the evolution of psychopharmacology in the United States over the last forty five years and Jerry's opinion of its future needs is an important part of the interview. He feels that Federal funds should be set aside "in some kind of a pool" to support worthwhile research not funded by industry, including comparisons of one drug with another and effectiveness studies of drug performance in routine practice, outside the artificial parameters of traditional controlled trials.

Jeffery Alan Lieberman s career in schizophrenia research spans the period between the time when the disorder was recognized as a genetically determined biological condition but still pessimistically viewed as "the cancer of mental illness" (1970-1990), followed by a decade of industry engendered false optimism (1990-2000) over "second generation" antipsychotic medications and finally leading up to the sober conclusions, fascinating insights and future predictions of the scientist who was Director of the landmark CATIE study which revealed, "our initial enthusiasm was wrong", a conclusion he describes in the interview as "a little bit of an Emperor's clothes phenomenon".

Jeff was born in 1948 and began his undergraduate education in Biology at Miami State University in Ohio on a full athletic scholarship. (The interview does not reveal his sport). It was a time (1970), when there was a "great cultural sort of ferment" epitomized by a course on the biochemistry of the brain where he was fascinated to learn that, "the thoughts or feelings people had were reducible to electrical charges and chemical molecules".

He entered medical school at George Washington University (1975) on a partial U.S. Health Professions Scholarship and won two awards in his final year; the William S. Schafirt Award for the best article on Medicine and Public

Policy and the Sandoz Award for outstanding achievement by a medical student in psychiatry.

Jeff had taken electives at NIMH as a medical student and while a psychiatric resident at St.Vincent's Hospital (NYU) he worked on a Phase II study of an antipsychotic as an elective in his fourth year. After graduation he began a Research Fellowship at Albert Einstein College of Medicine (1979-1980) at the time when Ed Sacher was Chair of Psychiatry and the Department was the leading neuroscience program in the country.

In 1980 he began his academic career as an Instructor in Psychiatry, working on tardive dyskinesia, leading naturally into research on dopamine and schizophrenia. Over the next 14 years (1982-1996) he moved steadily up the academic ladder, supported by NIMH grants, to become a full Professor (1992), Director of Research at Hillside Hospital and Co-Director of the Neuroimaging Laboratory at Long Island Jewish Medical Center.

During this time Jeff worked on the natural history and pathophysiology of schizophrenia, developing the methylphenidate challenge and using longitudinal neuroimaging techniques to study progressive structural changes in the brain.

In the early 1990's Jeff began to work with clozapine and recognized the unique clinical and biochemical properties that would spark the industry effort to synthesize similar compounds, leading to a Cinderella like decade between the introduction of risperidone (1993) and ziprasidone (2001). As Jeff describes it this was "a rather glorious period" during which schizophrenia, "having been a forgotten illness … suddenly became the darling". Clinicians and researchers were enthused and industry reaped vast profits. "We basically felt we were on the march to eradicate mental illness". Over a decade (1990-2000) the U.S. market in antipsychotic drugs grew from 500 million dollars to ten billion dollars.

In 1996 Dr. Lieberman moved to the University of North Carolina School of Medicine where he became the Thad and Alice Eure Distinguished Professor of Psychiatry, Pharmacology and Radiology (1996-2005). It was during this time that, "the bloom was coming off the rose". Clinicians began to question whether the second generation drugs were really better and worth their cost. Although they had less parkinsonian side effects they caused substantial metabolic consequences. At the same time the limitations of short term, tightly controlled, studies of selected populations were being recognized, coupled with industry's reluctance to perform comparative studies between the expensive new and generic older drugs, or between different second generation drugs. This led to recognition of the need for, "pragmatic or large sample" effectiveness studies of treatment outcome and side effects.

In October 1998 the NIMH began an application process for such a study, to cost sixty million dollars, the biggest contract ever awarded. When Jeff became Director of this multi-center study; “it was like mobilizing for war”. The study had three objectives, were the new drugs better than the old; how did the new drugs compare to one another; were they cost effective?” The details of how this was accomplished and the impact of the findings are related in the interview and were published in the New England Journal of Medicine in September, 2005.

This is a dramatic and significant story, perhaps the theme one day for a novel, but is not the sum and substance of Dr.Lieberman’s distinguished career. His lifetime research productivity has been prodigious. In 31 years (1979-2001) he was the Principal or Co-Investigator on almost twenty NIMH funded projects for over 25 million dollars (in addition to CATIE). He has also received substantial support from Foundations and Pharmaceutical companies.

For these individual studies and the body of his work he has received numerous honors, including a Merit Award (1990-1995) and an Independent Scientist Award (1995-2000) from NIMH; two Kampf Fund Awards in Psychobiological psychiatry (1994 and 2000) from the APA; The Alex Gralnick Award for research in Schizophrenia (1998); the APA Award for Research in Psychiatry (1998); the Ziskin-Somerfield Research Award from the Society of Biological Psychiatry (2001) and the Lily Neuroscience Award from the CINP (2002).

Dr.Lieberman has been a Consultant, Advisor, Task Force Member and Officer to numerous organizations including the APA, NIMH, DSM IV, WPA, FDA and the Society of Biological Psychiatry of which he was President (2004-2005). He is a fellow of the ACNP, a member since 1989, and active on a variety of its committees including Chair of the Credentials Committee (2004), and member of the Executive Council (1999-2001). He considers the ACNP, “the most prominent, prestigious and influential organization within the field … in the United States and possibly in the world”. He describes his first annual meeting as, “being like a kid in a toy store”, and he has attended every meeting since.

Since 2005 Dr.Lieberman has held positions at Columbia University as Laurence C. Kolb Professor and Chairman of Psychiatry, Director of the Lieber Center for Schizophrenia Research and Director of New York State Institute. He continues to be Director of the CATIE program for NIMH. Despite the disappointing (but enlightening) conclusions of that study he remains optimistic about the future of the field. He expects that, within a decade, the sequencing of the genome will lead to proteins and to new drugs so that, “we’ll have rational drug development”.

Douglas M. McNair was born in 1927 and, as a teenager during World War II, he decided to become a psychiatrist after reading Freud and Karl Menninger. To the great benefit of psychopharmacology events diverted him from this intention; his premedical College training was disrupted by the draft and when he returned to UNC at Chapel Hill he was attracted to a new V.A. training program for psychologists at the University.

Doug obtained his Ph.D. at the age of 27 in 1954, the dawn of psychopharmacology, and after a brief stint as a clinician opted for a research career working with Maury Lorr at the Outpatient Psychiatric Research Laboratory (OPRL), in Washington. His earliest research, comparing the outcome of various psychotherapy paradigms, was soon transformed into collaborative work with the V.A. on the first multi-center studies of the earliest psychotropic drugs, bringing him into contact with Leo Hollister who conducted this interview in 1997 and who had become first a mentor and then a collaborator.

The transition from psychotherapy to drug research was never total; “every study of psychopharmacology I was ever involved in included psychotherapy as a component”. Doug’s major contribution to the field was the development of valid and reliable rating scales and this too made a transition from early inpatient psychiatric rating scales (IMPS) to the Profile of Mood States (POMS) as drug research moved from State Hospitals to Community Clinics and from the measurement of symptoms to including “feeling and attitude scales”.

Dr.McNair worked with Lorr in Washington for eight years (1956- 1964) before moving to Boston University School of Medicine where he became Full Professor in 1970 at the age of 43, working in both Psychiatry and Psychology Departments and eventually becoming Director of Clinical Psychology Training in 1980. Throughout this time he and his colleagues continued to develop and revise POMS, including publication of several versions of the Manual over twenty years (1971-1992), with the later incorporation of Bipolar Mood States (1982). The POMS was used or cited in over 2,500 scientific articles and used in every branch of medicine (perhaps not radiology), including the Center for Mind-Body Medicine. Late in his career he became interested in the influence of anti-cholinergic side effects on memory and learning, particularly in the elderly.

Doug retired in 1991, at the age of 64 as Emeritus Professor but remained active, working for the Defense Department evaluating their demonstration project, training psychologists to prescribe psychotropic drugs, about which he was skeptical, “if you are a psychologist and want to prescribe drugs you would be better off going to medical school”. Ironically this was the path he chose not to take.

Doug became a member of the ACNP in 1966, was a Fellow Emeritus and a quietly enthusiastic, "under the radar" participant whose interesting views on the evolving role of psychologists in the organization are discussed in the interview. His hopes for the future lie in the development of effective drugs to treat violence and Alzheimer's disease, the two biggest challenges he sees facing our culture.

Doug McNair died in 2008 at age 81; in an Obituary his lifelong friend and colleague, Seymour Fisher, describes him as a "Tar Heel born and bred". In the Civil War Confederate soldiers of North Carolina were eulogized by General Lee for refusing to surrender or retreat, as if they had tar on their heels. More succinctly, Sy Fisher comments, "*During the many years I knew this remarkable man, I had nothing but total respect and admiration for his intelligence, dedication, modesty, and integrity. He was an avid reader who hated ambiguity and wrote with precision. His research was always impeccable when Doug published a paper, you could take the results to the bank. His students, his staff, his friends venerated him, and I always saw him as the favorite brother I never had.*

Doug was proud he came into our field when, "most people in Medicine sort of looked at psychiatry as almost anti-science" and at a time when our discipline "pioneered the field of trial methodology and was far ahead of the rest of medicine". This was an accomplishment to which Doug McNair made a major contribution.

John E. Overall s interview with Tom Ban in 2001 is a fascinating and detailed account of a long and distinguished career. It begins with his birth on the eve of the "Great Depression" and the travails this imposed on his family and childhood growing up in small town Texas.

While John describes himself as, "a late bloomer" who "didn't apply myself to studies in my undergraduate days", he developed a strong sense of self sufficiency fueled by amazing energy. From the age of 14 on he worked at a cattle auction barn, deck hand on a shrimp boat, travel agent at the Mexican border, as a collection agent for a loan company, on a railroad gang and had multiple paper routes! In addition he played for his high school football team, set track and field sports records and amused himself fishing and duck hunting.

After, "six years without receiving a degree" his life as a perennial undergraduate came to an end when his draft deferment was running out and he volunteered for the Air Force. His hope of staying at Lackland Air Force Base in San Antonio, close to his fiancé, was fulfilled and also determined the future of his career. The Base was home to the largest concentration of psychologists ever assembled, many of them academics, working in the Personnel Laboratory, developing measuring instruments for pilot selection.

John completed his service in 1954, graduating with a bachelor's degree in psychology at Trinity University in San Antonio before moving on to the University of Texas in Austin for his Master's (1956) and his Ph.D. (1958) in psychology by which time he had already done significant research and co-authored several publications.

John's interest in statistics began as a graduate student, working with Rhesus monkeys in the University Radiobiological Laboratory analyzing data from experiments on the effects of radiation on cognitive function. (The same lab where "Sam", the first monkey in space, was trained). His career in statistics was enabled by a National Science Foundation Postdoctoral Fellowship that he spent in the Psychometric Laboratory at UNC. (1958-1959).

The time had now arrived (1959) when the Veteran's Administration was undertaking the first controlled studies in the U.S. of chlorpromazine versus placebo, followed by a comparative study of six different phenothiazines. John accepted the job of Chief of Criterion Development at Perry Point V.A. in Maryland, leading to two important career relationships. With Donald Gorham as his mentor they developed the Brief Psychiatric Rating Scale (BPRS), published in 1962, and he began a twenty year collaboration with Leo Hollister in the design, implementation and analysis of psychotropic drug studies.

After two years at Perry Point (1959-1961) Dr. Overall seized the opportunity to fulfill his growing ambition to work in an academic environment by obtaining an NIMH Career Development Award and a faculty position at Kansas State University (1962-1963). When this concluded John decided to return to his roots and family, becoming an Associate Professor at the University of Texas in the combined Department of Neurology and Psychiatry at Galveston (1964), where he remained for fourteen years (1964-1978), becoming a Full Professor in 1967, just nine years after completing his Ph.D.

Dr.Overall's final career move was to the University of Texas Medical School in Houston as Professor of Psychiatry and Behavioral Science (1978-Present).

This interview provides details of the almost forty years between settling in academia and this interview (1963-2001). It has been filled with accomplishments, collaborations and relationships that read like a "Who's Who" of leading pioneers and scientists in the field of Neuropsychopharmacology. It includes the ECDEU, the ACNP, the CINP, the V.A, the F.D.A., the NIMH and WHO, all of which organizations he has served as a Consultant or Advisory Board member.

The latter part of the interview lays out Dr.Overall's philosophy and ideas about how best to help clinical investigators in, "understanding the complex statistical modeling procedures that are increasingly being promoted as state of the art for analysis of the types of data acquired in studies they design and

conduct". This is not easy reading for neophytes but, as John admits, his life's work has been guided by the principle that, "if it isn't novel or controversial it probably is not worth doing".

Eugene S. Paykel, like his Maudsley mentor, Aubrey Lewis, was raised in the Antipodes, studied psychiatry in leading British and American academic centers (London and Yale Universities) before becoming Professor and Head of a prestigious academic department, recognized for its research and educational accomplishment (Cambridge University).

As with a majority of successful, well known researchers, Gene has stuck to his last; "My heart lies in the controlled trial of antidepressants and other treatments of depression". In over forty years he has built an international reputation in the biological, social and psychological understanding of depression, attested to by a monument of over three hundred scientific publications (including two citation classics) and eight books.

The son of a Harvard trained business man and a New York concert pianist Gene was born (1934) and attended medical school (1951-1956) in New Zealand before he set sail for England as a ship's doctor on a cargo boat.

After several years training (1957-1962) and certification in internal medicine (The Royal College of Physicians), Gene completed his psychiatric education at the London Institute of Psychiatry, Maudsley Hospital, (1962-1966).

After graduating, and "still infected with wanderlust", he crossed the Atlantic to join Gerry Klerman at Yale University where they set up a Depression Research Unit, funded by a small NIMH grant and began work that laid the foundation for his career and reputation, (1967-1971). Included in his accomplishments was hiring Myrna Weissman whose subsequent marriage to Gerry created, "one of the most glowing marital partnerships in American academic psychiatry".

This interview by Tom Ban in 1999 details the research they undertook in that highly productive five year collaboration. Beginning with a cluster analysis and a new powerful computer they identified nosological subtypes of depressive disorder which banished the word "neurotic' from the psychiatric lexicon. Then they undertook a large epidemiological study with over nine hundred subjects (with the sociology department) that, for the first time, established a relationship between life events and the onset of depression. (A citation classic, published in the *Archives of General Psychiatry* in 1969).

Following this they became interested in relapse rates after treatment with antidepressants and demonstrated the contribution of drug treatment and Interpersonal Psychotherapy to preventing relapse and improving function. In 1971 Dr.Paykel returned to England to continue his career at St. George's Hospital in London, moving up the academic ladder as Senior Lecturer, Reader and Professor, (1971-1985). He continued the Yale collaboration but

also began his own line of research defining the characteristics of depression that responded to MAO Inhibitors and studying the treatment of mild depression in general practice with a tricyclic antidepressant. Gene was also involved in receptor binding and neuro-endocrine studies of depression but, "became disaffected with the platelet as a mirror of the brain".

In 1985 Dr.Paykel succeeded Sir Martin Roth as Professor and Head of Psychiatry at Cambridge University and, as is the British custom, was elected a Fellow of Gonville and Caius College (home to Francis Crick, Ronald Fisher and Stephen Hawkins). This interview again details several lines of productive research, (funded by the Medical Research Council), including the causes of early relapse and later recurrence of depression as well as Gene's leadership role as Chair of the Scientific Committee for an ambitious five year, "Defeat Depression Campaign", with an emphasis on identifying attitudes and beliefs that contribute to the publics' acceptance or rejection of treatment.

Apart from this continuing work on depression and bipolar disorder Gene was involved in epidemiological studies on the onset and course of dementia in the elderly.

Not surprisingly, this output has led to a reputation as, "one of the best-rated departments in Britain for our research".

Apart from research, teaching, mentoring and administrating a Department Gene confesses, "I like joining things". He is a Fellow Emeritus of the ACNP and has been President of the CINP, President of the British Association for Psychopharmacology, President of the Marce Society, and Vice-President of the Royal College of Psychiatrists (1994-1996).

Gene describes himself as a "bookish" man, (after all he married a librarian!), so it is not surprising he was founding Editor, with George Winokur, of *The Journal of Affective Disorders,* (1979-1993), and then became Editor of Psychological Medicine, (1994-).

Finally, on a lighter note, Gene comes from a musical family; his mother and two sisters have all been professional musicians. While he enjoys opera, theatre and music he has a "poor ear … my service to music is not to perform it". The music world's loss has been the scientific world's gain.

Frederic Quitkin, like so many of our psychopharmacology pioneers, was a child of the Depression, born in 1937, who came to adulthood on the cusp of the drug revolution when psychoanalysis still reigned supreme in American psychiatry. Subtly encouraged by intellectual parents to consider a research career he won a scholarship to Princeton as a Biology major (1956-1959) and wrote a biochemical thesis on the effect of urethane analogs on viruses.

Fred went to Medical School at Downstate, New York, (1959-1963) where he found psychiatry more interesting than pathology or medicine and briefly entertained the idea of becoming a psychotherapist. Fortunately he chose

Hillside Hospital for his residency where he was mentored by Don Klein and exposed to empirically based research at a time when, "clinicians … labeled virtually all patients schizophrenic". With Don's encouragement and help he wrote his first paper as a resident, showing how misdiagnosed, non psychotic patients, recovered rapidly after transfer to a State hospital but psychotic individuals lingered and deteriorated.

Now committed to a research career Fred assembled the tools by completing a Doctor of Medical Science degree at Downstate Medical Center where he took courses in research design and statistics, (1967-1969) before returning to Hillside for the next nine years (1969-1977) and working in collaboration with Arthur Rifkin, Don and Rachel Klein.

As related in this interview his career long research interests pursued three major themes. He demonstrated the subtle ("soft") neurologic impairments in schizophrenia, confirming that it was a biological brain disorder, not the childhood product of poor parenting. Fred also described the clinical features of "atypical" depression and its preferential response to MAO Inhibitors, an early demonstration of Don Klein's method of "pharmacological dissection". Thirdly he teased apart the characteristics which distinguished drug from placebo response which Don later described as, "a technical tour de force".

In 1977 Dr.Quitkin moved to N.Y. State Psychiatric Institute to establish his own independent "Depression Evaluation Service" and became Professor of Clinical Psychiatry at Columbia University College of Physicians and Surgeons. During his time at Columbia his research focus was almost entirely on depression, including the study of treatment response in people with comorbid alcohol and drug dependence.

Asked in the interview to comment on his career Dr.Quitkin remarks, "I deem myself as blessed. I try not to depend too much on drug companies and to have the opportunities to explore my intellectual curiosity". Altogether Fred published over 150 scientific articles and book chapters and collaborated with over 80 co-authors, many of whom he also mentored. He wrote or edited two books; the first early in his career, "*Diagnosis and Drug Treatment of Psychiatric Disorders ,* with Don Klein, Rachel Klein and Arthur Rifkin, is considered a classic (but now out of print) and more recently (1998) an edited multi-author text, *Current Psychotherapeutic Drugs* .

Among his broader interests Fred was a member of the ACNP (from 1975), the CINP and a Past President of the Psychiatric Research Society. He was also an expert skier, vigorous tennis player and an itinerant Francophile.

This interview, with Tom Ban, was recorded in 2001. At the end Fred says, "It's been a lot of fun. I wouldn't mind doing it for another forty years". Tragically it was not to be. Only four years later, (2005) he died at the age of

68 after a year long struggle with pancreatic cancer. In an obituary published in *Neuropsychopharmacology* (2006) his mentor and colleague, Don Klein sums up his friend, "He was a tireless clinical psychopharmacologist, never daunted by the most complex and difficult psychiatric disorders and always freely available to his many grateful patients for psychological support and vigorous pharmacologic treatment. His dedication and perseverance set an inspiring example for the pursuit of excellence in clinical research and therapeutic care".

Allen Raskin was another among a group of talented psychologists who participated in the development of research designs and rating scales for the pioneer multi-center studies at the V.A. Outpatient Research Laboratory in Washington D.C. and Perry Point Hospital in Maryland.

Born in 1926, Allen served two years in the U.S. Army at the end of World War II (1945-1946) before completing his undergraduate degree in psychology, *Magna Cum Laude*, from Syracuse University (1947-1949). Supported by a Public Health Service Scholarship he obtained his Ph.D. from the University of Illinois (1949-1954) which he characterized as , "a haven of dust bowl empiricism … that really had a strong emphasis on research and statistics" and where he published his first paper as a graduate student (1952).

After three years as a staff psychologist at a V.A. general hospital (1955-1958) Allen joined the Perry Point team (1958-1961) as a contemporary to John Overall who was developing the BPRS rating scale. In 1961 Allen took a position as Assistant Professor of Psychiatry at Georgetown University and became the Co-Principal Investigator of the six hospital V.A. controlled study comparing chlorpromazine to placebo. (1961-1964).

In 1964 he was invited to NIMH by Jonathon Cole and Sol Goldberg to join what became the Psychopharmacology Research Branch, where he remained for twelve years (1964-1986), becoming Chief of the Anxiety Disorders Section. His first task was to organize a ten hospital controlled study of over 500 depressed patients treated with chlorpromazine, imipramine of placebo. To do this Allen developed the eponymous, "Raskin Rating Scale", designed to measure the severity of depression on three items, verbal report, behavior and secondary symptoms. One index of the need for this was a huge discrepancy in duration of stay for "depressed" patients; the average in one hospital was 10 days while in another, psychodynamically oriented institution, relatives were invited to bring "seasonal changes of clothing". The Raskin Scale was widely used by industry for new drug studies after they modified it to measure change.

In 1986 Dr.Raskin retired from NIMH and moved to Detroit where he became Professor of Psychiatry and Adjunct Professor of Psychology at Wayne State University (1986-1988). During this time he worked with Sam Gershon

at the Lafayette Clinic on adolescent suicide attempts. Their finding that most of these were by young girls having trouble with boy friends might have delighted Shakespeare!

Allen's final career move as Research Professor at the University of Maryland (1988 -) brought him full circle back to his beginning and the disappointing realization that the staff at Perry Point V.A. had no institutional memory of the pioneer work in psychopharmacology performed there thirty years earlier.

This interview with Leo Hollister in 1997 brings together two colleagues and collaborators to reminisce about earlier times. Their dialog reinforces the value of an historical perspective. As they point out, computer literature searches seldom extend beyond ten years; stifling the nuances, insights, motivations and tribulations of the pioneers and burying their discoveries as "secondary citations" compiled by reviewers who have seldom read the original work.

Late in the interview Dr. Raskin says, "I kid myself and say that I am a Renaissance man because I have been in every area of psychopathology". The diversity of these interests includes his work as Editor of the Psychopharmacology Bulletin, member of the ACNP since 1970 (now Fellow Emeritus), Fellow of the American Psychological Society, Fellow of the American Psychopathological Society and Consultant or Committee Member to the FDA, VA and ADAMHA.

Karl Rickels is among a handful of surviving pioneers in our field with arguably the longest and most productive research career. At age 86 he remains active, has published almost 600 scientific articles and 9 books (still counting). It is an archive that began before Medline was born and which is remarkable, not so much for quantity, but for diversity, creativity and integrity.

How this came to be is equally remarkable. Karl was born in Germany in 1924 and was 15 when the Second World War erupted. He grew up in Berlin, was inducted into the German Army and captured by the Allies in North Africa as the tide of war began to turn (1943). He spent a year in America as a POW and describes his experience as follows; "I had a great time … I was treated very well. I enjoyed the Country. There was freedom of ideas and I always wanted to return".

Karl completed his medical school at Muenster University (1946-1951) followed by training in medicine, microbiology, radiology, serology and pathology (1952-1954).

In 1954 Karl left Germany for America, arriving at the same time as chlorpromazine. Like the drug's discovery his career was determined by serendipity when the first job he took was at a State Hospital in Cherokee, Iowa; at the time trans-orbital lobotomies were yielding to reserpine and chlorpromazine.

A year later he applied for residency at the University of Pennsylvania. Too poor to pay for travel he was accepted over the 'phone and has been there ever since, 55 years later.

Karl completed his psychiatric training in 1957; his competence must have been quickly recognized and his career expedited by early involvement in the NIMH Psychopharmacology Center where Jonathon Cole and Sy Fisher introduced him to Uhlenhuth, Covi and Lipman with whom he began to collaborate.

Like all the pioneers Karl recognized at once the virtue and superiority of drugs over therapy; he joined the CINP in 1958 (the year after it was founded) and the ACNP in its first full year of operation (1961). That charter class included 90 individuals of whom 66 are now deceased. Karl Rickels is one of the remaining 24 scientists who will hopefully celebrate the fiftieth anniversary of the ACNP in 2011. When Dr. Rickels became a Life Fellow in 2002 the Council and Credentials Committee expressed their, "special commendation for excellent, outstanding, service to the College and the field."

Many early psychopharmacologists who began working during America's love affair with psychoanalysis rejected it outright but Karl refused to throw out the baby with the bath water. His early research shows a special and valuable interest in the psychosocial as well as the neurobiological factors that influence drug response and his first edited book was, *Non- Specific Factors in Drug Therapy* (1968).

At the University of Pennsylvania Karl founded the Mood and Anxiety Research and Treatment Program over 30 years ago. Throughout that time it has been funded by NIMH, private corporations, Foundations and pharmaceutical companies while its research team identifies promising drug candidates in the field of affective and sleep disorders.

Many might consider this work a paradigm for what is necessary, but now almost absent; from commercial drug development, from the proceedings of the ACNP and from Federal funding priorities. That is, support for scrupulous, intensive, creative, inquisitive evaluations of newly minted compounds capable of linking structure, mechanism of action and function without conflict of interest, commercial bias or spin. Recently (2006) Dr. Rickels made the following comments, triggered by an earlier essay criticizing the misleading, oversimplified, advertising about putative mechanisms of action of the SSRI antidepressants, "… consumer advertising only focuses on expensive patented medications and not on equally good generic alternatives. Let's prohibit all, consumer advertising of patented medications. It will save physicians much headache, and patients or their insurers a great deal of money" ("*Consumer advertising can be misleading* - PLoS. Med.)

Given Dr. Rickels' philosophy, clinical acumen and integrity it is not surprising that he was recently awarded (2008) the *William Osler Patient Oriented Research Award.*

Dr. Rickel's research has included an encompassing range of topics. He participated in the development of the Hopkins Symptom Check List-25 which, like the GHQ, has been translated into many languages to facilitate the screening for psychiatric disorders in primary care, a field in which he has also undertaken collaborative research. This interview was conducted by David Healy in 1998, who has done similar work in Britain.

Much of Karl's early research was on ant-anxiety agents, beginning with meprobamate and graduating to the benzodiazepines. This included comparisons of short and long term treatment and the controversies around drug dependence that peaked in the 1970's. In this respect he believes the current backlash has gone too far; "I think Americans are Puritans, and maybe the people in Britain are Puritan's too". These issues are elaborated on in the interview.

D. Rickel's academic career is equally distinguished. He is Professor of both Psychiatry (1969) and Pharmacology (1976) and holds the Stuart and Emily BH Mudd Professor of Human Behavior and Reproduction. The duality of this title reflects yet another of his pervasive interests. His work in obstetrics and gynecology stems from involvement with non psychiatric patients in primary care and led to research in infertility and prevention of adolescent pregnancy. In 1993 he co-authored (with Ellen Freeman) the book, *Early Childbearing: Perspectives of Black Adolescents on Pregnancy, Abortion and Contraception .*

Karl spends his abundant energies in many different directions; he is Editor of Pharmacopsychiatry (1973 -) and is on the editorial boards or advisory committees of eight other leading journals in research, stress, primary care and neuropsychopharmacology. He serves on numerous University and Hospital committees and is a consultant, committee or task force member to pharmaceutical companies, AMA, NIMH, FDA, NIH, APA and the Academy of Sciences. If there is a single word to describe so talented a man it would be "polymath."

Alan F. Schatzberg comes from a medical family by way of Spain (Galicia) and Austria (Vienna). His father and two uncles graduated as physicians but were forced by escalating anti-Semitism in Vienna to practice as dentists (then a subspecialty of medicine). The family escaped to the United States before the outbreak of World War II, where Alan's father worked as a family doctor and his older sister became a psychiatrist.

Born in 1944, Alan grew up and was educated in the Bronx, completed his undergraduate degree at NYU (1965) and graduated from NYU School

of Medicine (1968). He did his psychiatric residency at Mass Mental Health Center (1969-1972) where he became Chief Resident and was mentored by Joe Shildkraut, subsequently a major career influence and collaborator.

Alan served the draft (1972-1974) as Major in the Air Force at the Pentagon helping develop substance abuse programs and improve race relations, tasks for which he received the Meritorious Service Medal.

This chronology places Alan in the second generation of psychopharmacologists and he joined the ACNP at age 39, in 1983. As related in this interview with Tom Ban in 2001, his innovative research has been at the cutting edge of new and exciting developments in the discipline and he has played a major role in the governance of the ACNP, as a Council member for seven years (1995-2002) and President (2000).

After military service Dr.Schatzberg returned to Harvard when he was recruited by Shervert Frazier to set up a depression unit at McLean Hospital where he was mentored by, and then collaborated with, Jonathan Cole and Joe Schildkraut. (1974-1988). In 1988 he became Clinical Director at Mass Mental Health Center and Full Professor at Harvard University. Three years later, in 1991, he was appointed the Kenneth T. Norris Professor of Psychiatry and Behavioral Science at Stanford University where he remains, after twenty years.

The interview details four major areas of research in depression; biogenic amine metabolism, Hypothalamic-Pituitary-Adrenal Axis dysfunction, psychopharmacologic treatments and the biology, etiology and nosology of psychotic depression. Much of this work has been funded by NIMH, including, more recently, a $600,000/year grant for ground breaking and controversial research into a potential treatment for cognitive impairment in delusional depression, (mifepristone or RU-486).

This body of research has yielded almost 700 scientific publications and 17 books in 36 years (1974-2010). Many of these articles have been in the field's most prestigious journals and the books begin with a single author text (now in paperback), "*Common Treatment Problems in Depression*", (1985), and leading up to the seventh edition of, *The Manual of Clinical Psychopharmacology ,* (2010), co-edited with Jonathan Cole and Charles DeBattista.

Dr. Schatzberg's research has also generated national recognition including; the *Gerald Klerman Lifetime Research Award* by NDMDA (1998); the *Gerald Klerman Award* from Cornell (2001); the *Edward Strecker Award* from the University of Pennsylvania (2001); the *Mood Disorders Research Award* from the American College of Psychiatrists (2002); the *American Psychiatric Association Award for Research* (2002); the *Distinguished Service in Psychiatry Award* from the American College of Psychiatrists (2005) and the

Chairman s Distinguished Scientist Award from Brown University (2007). In 2003 he was elected into the NAS Institute of Medicine.

Alan's enormous energy and diverse interests are spread among many areas; membership in numerous professional societies, hospital, medical school, regional and national committees, as well as editorial boards including, Co-Editor in Chief of *The Journal of Psychiatric Research,* Associate Editor in Chief of *Depression and Anxiety,* the *Journal of Clinical Psychopharmacology, Psychoneuroendocrinology* and *Biological Psychiatry.* He is President of *American Psychiatric Publishing Inc.,* Past President of the ACNP and Society of Biological Psychiatry, Secretary-General of the International Society of Psychoneuroendocrinology and, most recently, President of the American Psychiatric Association (2009-2010).

As Dr. Schatzberg was about to assume this most significant role in American Psychiatry he was drawn into a major controversy about the role of commercial influence on academic research, the seeds of which have been germinating for several decades but which became public during an enquiry initiated by Senator Grassley, *(New York Times, July 12, 2008).*

In the early days of psychopharmacology, almost fifty years ago, the drug treatment of mental illness was the orphan of a pharmaceutical industry that peddled panaceas, placebos and a few effective but toxic or addictive compounds. First generation psychopharmacologists did research for the fun or academic fame, supported by modest government funding or even smaller industry grants.

In five short decades industry became a multi-billion dollar purveyor of patented, expensive and effective remedies, advertised directly to an eager public. In the midst of this evolution, during the late 1970's and early 1980's, there was a slack interval in new drug development and Congress passed the Bayh-Dole Act with legislation intended to speed drug discovery by encouraging closer collaboration between academic research and industry.

An organization like the ACNP, committed to academic-industry collaboration and an accomplished, successful researcher and past president like Alan Schatzberg could hardly avoid being drawn into the crossfire over allegations of conflict of interest and undue commercial influence directed at organizations and individuals.

In the short term the controversy died down, stifled by strong support for Alan from Stanford and the APA, but underlying tensions remain. People are divided about the need for clearer, more open and stringent academic standards for disclosure and the need for stronger limits on the extent of commercial involvement in drug trials and their interpretation. The possibility of a win-win solution seems clear given that most clinical researchers recognize that lack of federal funding has led to declining creative academic

involvement in early drug studies with degradation in quality and a decreased likelihood of meaningful discoveries. Industry cannot afford to lose the skill, knowledge and effort of researchers in Alan Schatzberg's caliber.

In an address to the APA on behalf of its members David Kupfer describes the former President as "a compleat" physician, using that archaic term to convey someone who is unusually, "accomplished and consummate". Reviewing Alan's highly successful year as President, Kupfer elaborates, "I often think of Alan as a 'stealth' leader, a man with a quiet, unassuming manner who almost never calls attention to himself and, indeed, can be rather ironically self deprecating but who none the less gradually comes to command respect".

Nina R. Schooler is a pioneer in two senses; born in New York in 1934 she was a member of the first class of women (1951), admitted to the general study programs at the College of the City of New York (CCNY). She was also one of three women elected to the ACNP in 1975, doubling the total number of female members to six. Only 3 of 47 ACNP Presidents have been women, the first in 1988 (Eva Killam), 27 years after the ACNP was founded by an all male organizing committee.

Scientifically Nina has been a participant in almost all of the important research on schizophrenia over the last 37 years, beginning when Sol Goldberg recruited her as his part-time research assistant at the newly formed Psychopharmacology Service Center (PSC) set up by Jonathan Cole at NIMH (1963).

Nina's undergraduate degree was in anthropology (1955), supported by a New York State Regent's Scholarship and the Tremaine Scholarship from CCNY. Her graduate work in Social Psychology at Columbia University began in 1956 and continued part time for 13 years until her PhD in 1961 on language patterns in schizophrenia, based on the patient population in the first NIMH 9 hospital collaborative study of chlorpromazine and placebo, coordinated by Sol Goldberg and Nina.

When that study began Nina "didn't know anything about psychopharmacology" and she describes her feminine role, at a time of cultural "modest expectations", with a quote borrowed from George Bernard Shaw's description of women preachers; "It's like a dog walking on hind legs. You admire the fact that it does it and don't comment on the quality". But Nina was good at what she did; prior to NIMH she worked in market research, co-coordinating researchers and their data, "a task I've been doing ever since … but in other areas".

Surrounded by a cadre of the best psychopharmacologists in the field and with excellent mentoring from the likes of Cole, Klerman and Goldberg, Nina quickly gained skills, credibility and responsibility. Armed with her new

found title as “Dr.” he attended her first ACNP meeting in 1970, joined Sol’s study group on “Prediction of Response in Schizophrenia” and from then on (1971 -1988) she helped design and co-ordinate the NIMH sponsored series of drug studies in schizophrenia which set the benchmarks for future clinical practice. Nina notes, “I’m a really good collaborator and mentor”, talents predicted by a grade school report that, “she works well with others”.

The interview with Tom Ban in 2001 relates the sequential studies completed over 17 years, defining the short and long term effects of phenothiazines, optimal treatment regimens, relapse rates, compliance and placebo response and, ultimately, with Jerry Hogarty, the interaction of drug with psychosocial treatment.

Dr. Schooler retired from the NIMH in 1988 to become a full time academic at the University of Pittsburgh (1988-1997) where she was appointed Professor of Psychiatry (1992) and Professor of Psychology (1994) with the title of Director of Psychosis Research. She remained involved in bringing the NIMH studies to completion but also set up her own independent Special Studies Center at Mayview State Hospital where her research focused on treatment in both first episodes of schizophrenia and chronic refractory cases. In collaboration with industry she also began a series of studies on clozapine, and then other “second generation” anti-psychotics.

In 1997 Dr. Schooler moved to New York to join John Kane and became Director of Psychiatry Research at Zucker Hillside Hospital (1997-2003). In those five years she continued her work with second generation antipsychotics comparing clozapine with haloperidol and risperidone with olanzapine. She also worked with NMDA agonists in treatment, focusing on negative symptoms.

After New York, Dr. Schooler moved her base of operations to the VA Medical Center in Washington DC to become Senior Research Psychologist (2004-Present) with academic appointments as Professor of Psychiatry at SUNY and Adjunct Professor of Psychiatry and Senior Psychiatric Neuroscientist at Georgetown University School of Medicine (2004-Present). Consistent with her lifelong pattern of collaboration and continuity she maintains academic and collaborative relationships in both Pittsburgh and New York.

Throughout her independent (post NIMH) career Dr. Schooler’s research has been supported by 14 NIMH grants (2 current) and 16 industry projects (2 current).

The full measure of what Nina would make of her encompassing experiences and unique career were not clear at the time her interview took place in 2001. The subsequent decade (2001 – present) has been a period of remarkable productivity and expanding influence during which Nina remains fully

active at an age when many colleagues and contemporaries have long since retired. Comparing the first half of her career (1966-1983) with the second (1984-present) the number of her scientific publications has quadrupled (26 to 104) and book chapters have tripled (8 to 22). The topics in this literature cover her personal involvement in virtually every aspect of schizophrenia, its treatment and outcome.

In the last ten years Dr. Schooler has been active in sharing and disseminating her extraordinary knowledge of the field. In addition to teaching medical students, psychiatric residents and psychology interns in her hospital and university settings she has been a guest lecturer or visiting professor in 18 foreign countries (Europe, Asia, Africa, South America and Scandinavia), and 23 states in America.

In addition to research, teaching and her continuing collaborations Dr. Schooler participates actively in the professional arena. She is a Fellow and Past President (2000) of the American Psychopathological Association; Fellow and Past President (1991-1993) of the Association for Clinical Psychosocial Research; Fellow and Council Member (2004-2010) of the CINP and she has been a member of 8 ACNP Committees over 30 years (1979-2010).

Nina has served on the Editorial Boards of five journals and is a reviewer for many more; she is active in NAMI and NARSAD and an advisor to the APA DSM task forces on tardive dyskinesia, psychotic disorders and schizophrenia. She has been a consultant and member of work groups, research and advisory panels, review committees and study sections for the NIMH, VA and FDA.

At the end of his interview in 2001 Tom Ban's final comment is, "you seem to intend to keep on going". Never were truer words spoken!

George M. Simpson was born in Pennsylvania in 1926 to Scottish parents and returned to his family homeland as a young lad following the death of his father (an electrician in the coal mines). After a "wilder" than usual adolescence he completed high school in Lanarkshire (1940) before achieving a leisurely undergraduate degree in biochemistry from Glasgow University (1948).

With the war over, life began in earnest when the draft board assigned George work of "national importance" (1948-1950) with the Distillers Company in Liverpool which produced 33 varieties of whisky and 2 antibiotics. Work on fermentation of the healthier product and having a shared ancestry with the Dean of the Medical School achieved admission to the program and he graduated as a physician in 1955 at age 29.

A job ad. in the Lancet from McGill University lured George back to North America when Ewen Cameron, (more ancestry?), accepted him by letter, sight unseen, into one of the most exciting and eclectic psychiatric programs at the dawn of psychopharmacology (1955). Innovative faculty with diverse

interests mentored an outstanding cadre of trainees, thirteen of whom later became chairmen of departments.

This interview, with Leo Hollister (in 1994), displays both George's skill as a raconteur as well as a self-effacing sense of humor. After a period in Montreal (1956-1957) as an Assistant Resident he took a step that would place him at the cutting edge of the new and developing field of research in clinical psychopharmacology. He negotiated by 'phone with Nate Klein whose, "hard sell" encouraged him to join "a somewhat eccentric group" of fellow researchers. This allowed George to complete residency (1957-1959), earn a modest living wage ($300 a month) and begin to fashion an American identity.

It also marked the start of a highly productive and unusually lengthy career. Now an octogenarian Dr. Simpson remains active as Professor of Research Psychiatry at LAC and USC School of Medicine, publishing more than thirty articles in the last seven years (2003-2010).

George's early work at Rockland State was colored by Nate Kline's unusual blend of creativity and entrepreneurship. The hospital provided a pool for work with thousands of schizophrenic and psychotic patients on drugs like reserpine and chlorpromazine while Nate's New York private practice offered hundreds of depressed patients eager to try the new antidepressants, first the MAO inhibitors and then the tricyclic compounds.

While this work brought Nate the fame he sought (Two Lasker Awards) it introduced George to Jonathon Cole at NIMH and to becoming one of the early ECDEU investigators supported by Federal grants. The result was a productive blend of clinical acumen and increasing research sophistication. "With a very small number of patients we were able to show that it was or was not an active anti-psychotic agent. Probably (Art) Sugarman and (Don) Gallant and I looked at every anti-psychotic we have today before it came on the market. We knew our patients very well and since we saw them every day it was not really very difficult to tell whether a drug was active or not … I could confidently state whether a drug was active and whether it produced EPS with a sample size of ten patients".

This last comment highlights the scientific brush strokes George has added to the clinical canvas. Beginning in 1960, with the support and resources of the ECDEU he began to introduce rating scales into Rockland State's research. Perhaps his greatest contribution to the field has been the Simpson-Angus Extrapyramidal Side Effects Scale (ESRS). This measures ten extrapyramidal features, each on a four point scale. Published in *Acta Psychiatrica Scandinavica,* (1970), it remains the most widely used measuring instrument for its purpose forty years later. While it has been criticized for less than per-

fect psychometric properties and under emphasis on bradykinesia its elegant simplicity and ease of administration ensure its continuing popularity.

Dr. Simpson remained at Rockland State for twenty years (1957-1977) serving as Principal Research Psychiatrist for half that time (1968-1977) and attaining the academic rank of Associate Clinical professor at New York Medical College, (1974-1977).

As detailed in the interview he then moved to UCLA as Professor of Psychiatry for five years (1977-1983) before a seven year stint as Professor of Psychiatry and Pharmacology and Director of Clinical Psychopharmacology at the Medical College of Pennsylvania, in Philadelphia.

In 1994 he made the last major move of his career, returning to UCLA as Professor of Research Psychiatry and Director of Clinical Research in the School of Medicine where he remains today.

Throughout his career George has been active in the ACNP. He became a member in 1965 (now Life Fellow Emeritus), served as a Council member (1990-1992) and as President in 1991.

Dr. Simpson's substantial contributions to research in schizophrenia and depression have garnered national and international recognition. He received the Arthur P. Noyes Award in 1991, an Honorary Doctorate of Medicine from the University of Goteborg in Sweden in 1994, and the Heinz Lehman Research Award in 1999. He also received a 10 year Merit Award from the NIMH for his pioneer research on Clozapine in Treatment Resistant Schizophrenia.

Dr. Simpson has served on numerous Committees and Task Forces for a variety of organizations including HEW, FDA, NIMH, the APA and the ACNP. He is a member of numerous professional organizations and was elected Honorary President of the Egyptian Psychiatric association in 2003.

Finally, those who know George well would consider no description complete without mentioning his distinction as a gourmet, oenophile and connoisseur of his ancestral libation. So, naturally, he speaks French and has close friends in New Orleans.

Eberhard Uhlenhuth, known to friends and colleagues as "Uhli", is of German ancestry but was born in the United States, at Baltimore in 1927. After an undergraduate degree in Chemistry from Yale (1947), he completed medical training, (1947-1951), and psychiatry (1952-1956), at Johns Hopkins University, ending as Chief Resident.

As was customary at that time he also spent nine years (1957-1966) as a student at the Baltimore Psychoanalytic Institute and his training was predominantly inpatient and psychotherapeutically based with some patients hospitalized for years.

This was on the cusp of change; Jerome Frank, Uhli's mentor, and a leader in psychoanalytic theory developed the Hopkins Symptom Check List

(SCL 90) which, paradoxically, became widely used in the first psychopharmacology studies at a time when the Psychopharmacology Service Center at NIMH was initiating the earliest collaborative studies under Sy Fisher and Jonathon Cole.

As told in the interview, Uhli became involved in a comparison of meprobamate, phenobarbital and placebo when outcomes were still ascribed largely to psychodynamic factors and drugs were considered "adjunctive agents". Like Karl Rickels, these evolving paradigms shaped Uhli's early interest in "non drug factors". Not until the Harris-Kefauver Amendments in Congress (1962), in the wake of thalidomide, did the FDA, influenced by Lou Lasagna (also at Hopkins), begin to require placebo controlled studies that proved the efficacy of drugs as pharmacological agents. This turned Uhli from skeptic to believer.

Collaborating for five years with David Duncan in the School of Hygiene and Public Health Uhli developed statistical skills and co-wrote the first computer program for multiple co-variance analysis of data, a tool that facilitated continuing work with Mitch Balter at NIMH on the interaction of pharmacological and psychosocial outcome factors.

After 12 years at his alma mater Uhli was recruited by Dan Freedman to the University of Chicago (1968-1985) where he became Chief of the Adult Psychiatry Clinic and ,later, Full Professor of Psychiatry (!973-1985) and Clinical Pharmacology (1975-1985). During this time 11 out of 15 of his research grants were government supported (and 4 by Industry) on a wide range of topics including investigational drugs, life stress and personality factors in cervical cancer, drug interactions, panic disorder, national trends in psychotropic drug use and a cross cultural study of somatic symptoms and thinking styles. He also worked with Gene Paykel on the development of life event scales which would establish their role in the onset of depression (published in *Archives of General Psychiatry,* 1973). Included in this period were a USPHS Research Scientist Award (1976-1981) and a Psychiatry Research Training Program Award (1982-1986).

In 1986 Uhli moved to the University of New Mexico where he is now Distinguished Professor of Psychiatry Emeritus (2005 – present). In the early days at New Mexico Uhli co-edited a book with Sy Fisher and Al Raskin on Cocaine (*Oxford University Press,* 1987). During his time in New Mexico all 11 of his research projects have been funded by pharmaceutical companies but the topics have remained diverse including investigational drugs from Phase 1 (dose finding), to Phase 4 (post marketing surveillance for benefits and side effects) as well as national and international surveys on expert's attitudes and the use of psychotherapeutic drugs.

Dr.Uhlenhuth's distinguished career began sixty years ago (1951) and he remains active at age 83. When he became a psychiatrist (1956) the discipline in America was predominantly a speculative mythology which he helped transform into a statistically driven science. He was a founding member of the ACNP (1961), now a Life Fellow Emeritus. Uhli was a Council member (1985-1987) and President of the organization in 1986, also a time of profound change as the Federal Government gradually switched its funding emphasis to basic neuroscience and industry established its hegemony over clinical research. Through all these changes Dr. Uhlenhuth's lifetime contributions have included almost every area of clinical psychopharmacolgy

Oldrich Vinar s remarkable career, from his birth in 1925 until today, spans the troubled history of two cultures, the Czechs and the Slovenes. United at the end of World War I (First Republic 1918-1938), annexed by Germany in World War II (1939-1944), occupied by the Russian Army in 1944 and ruled by the Communists from 1948 until the Velvet Revolution (1989) which led to a brief period of unified democracy (1989-1992) followed by a peaceful dissolution into a rebirth of the original Czech and Slovak Republics (1993), still in existence today.

Against this background Oldrich graduated from medical school at Charles University in Prague in 1949, aged 24, a time when the medical profession had been almost eradicated by closure of the Universities during war time with the incarceration and death of many Jewish physicians in Nazi concentration camps. This left only forty psychiatrists for a population of twelve million people.

Oldrich's ambition to be a neurologist was thwarted when the Ministry of Health assigned him to a "Hospital for Brain Diseases" in a small village north of Prague that proved to be a mental institution, where he joined the only other doctor. With no training in psychiatry he shared the responsibility for eleven hundred patients to whom they provided obstetric, dental, X-ray and general medical services. Many psychotic patients had been castrated for "eugenic" reasons.

For five years, before the advent or reserpine or chlorpromazine in 1954, treatment consisted of "Pavlovian psychiatry" with prolonged sleep therapy ("protective inhibition") induced by bromides, barbiturates and antihistamines. Caffeine was for apathetic patients and ECT (at first without anesthesia or muscle relaxation) for aggressive or violent patients. Even the neuroleptics were slow to take hold for economic and ideological reasons. Pavlovian theory located the mind and its aberrations in the cortex which required semantic revisionism to "block the (subcortical) 'bad boy' so the cortex could win".

Fortunately for psychopharmacology Dr.Vinar was soon transferred to the Postgraduate Institute of Medicine in Prague where he worked in the Department of Psychiatry in collaboration with the Institute of Pharmacy and Biochemistry as well as the Czechoslovakian Pharmaceutical Industry.

Not widely recognized, but remarkable given the circumstances he was working under, Dr.Vinar's early contributions to psychopharmacology were in advance of developments in America. By 1958 he had begun to introduce controlled clinical trials, the use of rating scales and to organize annual interdisciplinary meetings of clinicians and pharmacologists to exchange data. (Three years before the ACNP was founded for the same purpose). In the same year (1958) Oldrich tested a new antihistamine with powerful antiemetic properties as an anti-psychotic (moxastine teoclate). In 1961 he developed the first package for multi-center studies, similar to the VA protocols in the USA, and in 1961 he co-edited (with Votava) a text on *Psychopharmacological Methods* (Pergamon Press).

Most of the earliest human trials of putative new psychotropic drugs developed in Prague were carried out by researchers on themselves. Employees at the Institute of Pharmacy and Biochemistry knew when Protiva (a chemist) had synthesized a new drug because Professor Votava (a pharmacologist) was found unconscious in the corridor. Oldrich himself took psychedelic drugs until he endured a psychotic state that lasted nearly three days.

Dr.Vinar became a Fellow of the CINP in 1966 and presented papers on EEG methods of drug evaluation and selection at early meetings. In 1969 Tom Ban, Don Klein and Jerry Levine facilitated Dr.Vinar spending half a year in the Biometric Laboratory at George Washington University, in collaboration with NIMH. In1971 he co-edited a second text (with Votava and Bradley) on *Advances in Neuropsychopharmacology* (North Holland Publishing Co.)

Dr.Vinar's scientific productivity is all the more remarkable because it was conducted under a Communist regime which sometimes forbade him from attending meetings and seldom financed his trips adequately. So he would purchase an advance unrestricted travel ticket that lasted six weeks and allowed him to eat and sleep free in the sky.

This interview with Leo Hollister in 1995 provides further details of Dr.Vinar's later research activities under the Communists. Not everything was negative. When, like his American counterparts, he recognized the way in which individual differences and unreliable clinical diagnoses made it impossible to choose "the right drug for the right patient" he was able to capitalize on the conformity of a system that treated all patients alike and inflicted universal double blind conditions. This allowed him to amass data on eight to nine hundred patients with schizophrenia and six to seven hundred with depression. This created an opportunity to identify correlations between

receptor affinities of drugs and therapeutic effects on clinical symptoms, independent of nosology.

The counterpoint to this advantage of working in a totalitarian system was that the Director of the Institute took a dislike to his work and theories, exerted political influence and threw him out of his job so he ended up working as the doorman in a hotel (1978). Worse still, they destroyed his data.

The interview ends with interesting philosophical insights. Asked to summarize his career Oldrich has this to say, "I never have thought of my career … I was … too involved in the questions to which I wished to find an answer. I am just curious, so curious it has become a handicap". He is always moving ahead of his latest idea in search of the next. Now he is 85, living in a free society. Who knows what may be next.

David Wheatley s role in the developing field of psychopharmacology was unusual and unique in several ways. Like his interviewer, Leo Hollister, David was not a psychiatrist but began his career in general medicine. After training at Cambridge University and Guy's Hospital he became a general practitioner in London. He quickly realized he was more interested in drug research and developed a consortium of 500 like minded family doctors from all over Britain.

Born in 1919, David was 35 by the time chlorpromazine began to be clinically tested in psychotic hospitalized patients (1955) and 40 when the first antidepressants and minor tranquilizers began to make an impact in family practice (1960). This is the age at which the literature suggests that research creativity begins to wane but David saw and seized the opportunity to turn his group's interests towards psychopharmacology, changing the name from the General Practitioner Research Group to the Psychopharmacology Research Group, the first national collaborative enterprise of its kind in the world.

David was introduced to Jonathan Cole by a contact in the pharmaceutical industry at the time when the ECDEU was being formed in America. This was when family doctors in the States were uninterested in research while conditions were conducive in Britain, facilitated by a universal system of health care. As subsequent events proved, minor or early affective disorders are common in primary care settings and that patient population consumes the bulk of psychotropic drugs for depression and anxiety.

The result of this confluence of interests was that David Wheatley's group became the only ECDEU (later NCDEU) research center outside North America, directed by a British general practitioner, and funded by NIMH for 12 years.

This cross cultural collaboration bore valuable fruit; The UK Research Group benefited from sophisticated research designs and valid rating scales while the ECDEU gained valuable experience and data in non hospital

outpatient settings. Part of the 'quid pro quo' was a requirement that Dr. Wheatley participates in regular ECDEU planning sessions and attends annual ACNP meetings.

This latter requirement also proved productive. Impressed by the vision and mission of the ACNP David set out to develop a comparable organization in Britain, the British Academy of Psychopharmacology (BAP) of which he was a co-founder and first Honorary Secretary.

This interview, in 1997, contains reminiscences between colleagues from two different cultures with much in common. Together they discuss the changes they have lived through as clinical researchers and as participants in ACNP meetings over the years. Not unexpectedly they echo concerns expressed in other interviews in the series. The dominance of industry, particularly in funding research, the loss of personal involvement in design, analysis, interpretation and publication of data, the growing hegemony of basic over clinical research and a loss of informality in ACNP organizational affairs.

For all the similarity between the two pioneers, both now deceased, (Hollister in 2000 and Wheatley in 2007), one difference stands out. Leo Hollister was a Founding Member of the ACNP (1961) and served as its President (1974), a distinction not achieved by David Wheatley in Britain. His obituary by former BAP President Merton Sandler, (1980-1982), includes the following, "I am sad we didn't make him President at some stage. Well, the Zeitgeist wasn't right then for a mere General Practitioner to be given the honor of heading a serious learned society". What a sad oversight!

Andrew Winokur is among an increasing proportion of ACNP members with both an M.D. and Ph.D. This interview by Andrea Tone in 2004 tells an intriguing and inspiring story of how someone who began as an American Studies undergraduate major at Yale (1962-1966), with no interest in medicine, evolved into a leading scientist in neuropsychopharmacology.

American Studies laid the groundwork for, "pulling information from a lot of disciplines together" coupled with an ability to express thoughts and ideas in writing. But the spark that kindled an interest and dedication to psychiatry was ignited when Andy enrolled as a volunteer (1962-1963) at Connecticut Valley State Mental Hospital and was paired with a young male with schizophrenia who was his own age with whom he developed "over the years a strong bond".

As he shifted into pre-med courses he enjoyed psychology, found organic chemistry and physics a "tremendous effort" but was inspired to continue when a Yale anatomy professor, (Jose Delgado), dressed as a matador, stopped a charging bull in its tracks by triggering an electrode implanted in the amygdala.

A “light bulb went on” and Andy entered Tufts Medical School determined to “pursue a career in psychopharmacology and biological psychiatry”. He discovered this was a poor choice of schools when the Chairman of Psychiatry interpreted his desire to do research as a neurosis and defense mechanism to avoid getting close to patients. Undeterred, Andy sought alternative experiences and spent the summer between his second and third years and a fourth year elective working in Joe Schildkraut’s lab at Mass Mental Health Center. This work, on norepinephrine turnover in rat brain following long term administration of imipramine, was published in *Science* with A. Winokur as the second author, in his final year of medical school (1970).

Andy’s choice of a residency program was more appropriate; at the University of Pennsylvania he obtained rigorous training in both psychiatry and pharmacology, (1972-1976), during which time he had two further publications including as first author in *Science* (1974) on the regional distribution of TRH in rat brain. Andy finished his final year of psychiatry as Chief Resident (1976).

It is difficult to imagine a more purpose driven start to a career that led to a quarter century (1971-1997) of clinical work, research and teaching in psychiatry and pharmacology at Pennsylvania School of Medicine during which he climbed the academic ladder, attaining the rank of Full Professor in both disciplines in 1998, at age 44. During this period Dr. Winokur’s core interest remained in translational research but expanded from neuroendocrine function in the brain to include sleep disorders and dependency on benzodiazepines.

In 1997 Dr.Winokur moved briefly to Dartmouth Medical School to work with Leighton Huey whose, “innovative cutting edge ideas about psychiatry” he admired and shared. Together they left Dartmouth after a year when Dr. Huey became Chair at the University of Connecticut, where Andy has remained, (1998-present). He is Director of the Neuropsychopharmacology Treatment, Research and Training Center. In 2006 he was named Dr. Manfred J. Sakel Distinguished Chair of Psychiatry and recently (2010) he became Co-Director of the Psychopharmacology Course for residents at the Institute of Living.

Dr. Winokur is the author of over 100 scientific publications, 35 book chapters and has co-edited two texts, *Behavioral Bases of Psychiatric Disorders* (Spectrum Publications, 1977) and “*Biological Bases of Brain Function* (Raven Press 1994).

He is the recipient of numerous awards for this body of research. Between 1975 and 1990 he received three consecutive multi-year NIMH Research Scientist Awards, followed by the NARSAD Senior Investigator Award (1993-1994) and the NAMI Exemplary Psychiatrist Award (2009). He is also a much

admired teacher. In 1987 he received the Earl D. Bond Award for Excellence in Teaching (Department of Psychiatry) and for three consecutive years (2007-2009) was awarded the Resident's Choice Teaching Award. He is justifiably proud of the fact that 10% of the medical student class chooses psychiatry as a career.

Throughout his career Dr.Winokur has served on numerous local and regional academic committees and has been a consultant and member of national advisory and review committees for the VA, APA, NIMH and FDA.

As told in the interview, Andy is optimistic and enthusiastic about the future of psychiatry and firmly believes the ACNP "provides us with clear and accurate and indelible road maps for where we need to be going." His own career is an exemplar of the formula on which the organization was founded; interdisciplinary collaboration leading to translational research and findings that will benefit patients.

INTERVIEWEES & INTERVIEWERS

JOSEPH AUTRY III

Interviewed by Leo E. Hollister
Washington, DC, April 15, 1997

LH: Today is April 15th, Tuesday, 1997. We are in Washington, DC, and doing a series of tapes, sponsored by the American College of Neuropsychopharmacology. I'm Leo Hollister, and my guest today is Dr. Joseph Autry.* Welcome, Dr. Autry.

JA: Thank you.

LH: First of all, I detect a somewhat different accent from the usual American accent and in looking over your CV I found that you graduated from the University of Rhodes, which I didn't recognize as an American University. Is that Rhodesia?

JA: No, it's Rhodes University in Memphis, Tennessee.

LH: Really?

JA: It's a small private Presbyterian college.

LH: I'll be damned. That really surprises me. So, Memphis, TN, and then you went to the University of Tennessee for your MD degree.

JA: That's correct.

LH: And how did you get into psychiatry?

JA: Well, I guess it started in undergraduate school. I started out majoring in chemistry and math; got bored with math and picked up a second major in psychology. I became interested in doing experiments in psychology and realized I could combine chemistry and psychology if I went into medicine and into psychiatry. I wanted to be able to use medications to help treat psychological disorders.

LH: So, your interest primarily was in the psychological area, but you figured medicine was a better entry into what you wanted to do in it.

JA: Right.

LA: And then what did you do?

JA: I went to the University of Tennessee Medical School, got involved in research there in the early days of using lithium to treat bipolar illness and then started on an NIMH fellowship and worked in the area of immunoglobulin research in schizophrenia for a couple of years.

LH: Was that also at Tennessee?

JA: That was also at the University of Tennessee. Then I did a straight medicine internship at Baptist Memorial Hospital; came to the National Institute of Mental Health in their old model residency training program;

---

* Joseph Autry III was born in Pine Bluff, Arkansas in 1943.

went from there into the Center for Studies of Schizophrenia, and into research.

LH: So, early in your career, then, you were involved in both, treating bipolar illness and later schizophrenia.

JA: That's correct.

LH: What were the drugs in use at that time for schizophrenia?

JA: The primary ones we had were the phenothiazines, most notably, Thorazine or chlorpromazine, and Stelazine or trifluoperazine.

LH: What date was that?

JA: That would have been in the late 1960s, early '70s. Haloperidol was one of the key drugs that came on the scene late in that period of time.

LH: Chlorpromazine was really the first landmark. I guess haloperidol was in a lesser way.

JA: Right.

LH: As all of them are lesser. The difference between having chlorpromazine and not having chlorpromazine was a major change.

JA: That was night and day. It certainly changed the treatment for schizophrenia in that period of time.

LH: And then what did you start doing?

JA: After my residency, I became chief of psychiatry at the Naval Operations Base in Norfolk, Virginia, for two years, and then came back to NIMH in 1975. I headed the depression section in the extramural research program, started the behavioral medicine and psychobiological processes program, and then the mental health clinical research centers program.

LH: I see. Can you tell me a little more about each of those?

JA: That's ancient history now.

LH: I'm not too familiar with them.

JA: In the depression program and the clinical research program, we were looking at the etiology of depression, working to diagnose and categorize mental illnesses better, including the affective disorders. We looked at the genetics underlying the depressive disorders and developed instruments for measuring change in depressive symptomatology in conjunction with the psychopharmacology program of Al Raskin and Jerry Levine. And in the behavioral medicine and psychobiological processes program, we were interested primarily in disorders like anorexia nervosa, bulimia, looking at behavioral correlates of these disorders, and for sequelae of physical disorders such as diabetes mellitus and cardiovascular disorders. The mental health clinical research centers program was the first program that NIMH sponsored that funded both basic and clinical research at the same institution trying to form a bridge

between the basic sciences and the clinical sciences. It has been a very, very successful program over the years.

LH: Very necessary, too.

JA: Yes.

LH: Now, were these intramural or extramural programs?

JA: These were extramural programs. I did some research of my own in that period of time looking at the influence of drugs in the treatment of depression, and then comparing drug treatment with psychological treatment in depression, working with Morris Parloff and Irene Waskow.

LH: Was this part of the emphasis on depression that occurred when Gerry Klerman was director of ADAMHA?

JA: That was part of it. Gerry was one of the investigators working with Myrna Weissman, who worked in the program where we had two short-term forms of psychotherapy, cognitive behavior therapy and interpersonal psychotherapy, compared to drug treatment, looking at the benefits in depression. And to everybody's surprise, we actually found that they both worked very well, the short-term psychotherapy interventions as well as the drugs. We now know, of course, that the combination of psychotherapy and medication works better than either one of them on its own.

NH: That makes sense.

JA: Yes, it does. But sometimes you have to do the research to prove what makes sense.

LH: I think that report was criticized. The drugs worked better in more severe depression.

JA: That's correct.

LH: And the psychological treatments were more effective in the less severe depression. I suppose in practice that might be translated to say that when someone is seriously depressed the first line of treatment should be with drugs, and as patients come out of depression, to get long lasting effect, one should try the interpersonal and social kind of therapy that Gerry and Myrna were interested in. Is that a correct interpretation?

JA: I think it is a correct interpretation, but I also think that what we have seen in clinical practice is that there is an evolution to using medication more frequently in more patients so that even for moderate depression or even fairly minor depression now, a number of people use drugs as part of their first line of attack on depression.

LH: Yes, but despite all the emphasis that NIMH has placed on depression, I recently ran into Bob Hirschfeld's article in JAMA about the undertreatment of depression. It still exists.

JA: It still exists. You have to remember that tertiary specialists, like psychiatrists only see about 20% of the people who are depressed and, hence, they prescribe only about 20% of the medication that is used for depression. Most treatment for depression is still carried out by primary care physicians. I think as newer generation antidepressants have come on line that have less side effects than the ones of the older generation, you are seeing more and more primary care physicians using pharmacological treatment. Unfortunately, I think they tend to under prescribe or under dose when they use medication. And a lot of times they just flat out miss the diagnosis of depression.

LH: As you said, they probably under diagnose.

JA: That's correct.

LH: It's so subtle because hardly anybody comes in and says, gee, I feel depressed, you know. They come in with a variety of somatic complaints that can lead you down a lot of blind alleys.

JA: In talking to my internist friends, they say that probably 40 to 50% of the patients that they see have some significant component of depression or anxiety disorder.

LH: It is interesting that you have mentioned the two together, because for many years John Overall and I were doing studies in depression, and we found that anxiety was just as frequent and just as severe in depressed patients as depression.

JA: I think that's absolutely correct. I think you also are seeing that many of the antidepressants have, in turn, been used to treat anxiety disorders over the past several years.

LH: I think Ron Lipman did a study some years back in which he showed that imipramine was equivalent to one of the benzodiazepines, I forget which one, in anxious patients. The only trouble is, it's much easier to take the benzodiazepine.

JA: Absolutely.

LH: Tricyclics are not too pleasant to take for patients who are not depressed. So, now you've covered depression, schizophrenia and anxiety. What else have you been into?

JA: Well, we worked on post-traumatic stress disorder (PTSD) for awhile with Jack Masur. That was at a time when there was very little research on PTSD. We actually found that it was a very definable syndrome and one that was amenable to treatment, both with psychotherapy and also with medication. I think probably the biggest advance we made was not in the psychopharmacology area, interestingly enough, but in the area of diagnosis and eventually developing DSM-III, DSM-IIIR and DSM-IV. I think that has really revolutionized psychiatry in this country.

LH: Yes. PTSD is certainly not limited to Vietnam War veterans.
JA: Absolutely not.
LH: It can occur in everyday life, that some terrible thing happens, and people get involved in it. So what is the drug treatment of choice for that?
JA: It depends on the symptomatology. Many times you can use an antidepressant or a combination of an antidepressant and a benzodiazepine, and it works quite effectively for those folks.
LH: Speaking of benzodiazepines and depression, have you ever been convinced that alprazolam has any special benefits in depression?
JA: I have read the studies, but I have not seen it happen clinically when I've tried to use it that way.
LH: Another thing that I have always been puzzled about is panic disorder that Don Klein first started talking about in the 1960s, which I think is a new name for an old phenomenon. It was not until 1980 or so, that panic disorder became epidemic. It happened to coincide with the development of alprazolam that was looking for a niche in treatment and came up with panic disorder. But that is probably blind speculation.
JA: Well, I don't know that it is necessarily speculation. I sometimes think that disorders do follow the availability of drugs rather than the other way around.
LH: That's a good way to put it. So, God, you've had your hand in a lot of different things. Now, your role in these was to put out contracts or just put out word that grants would be available in these areas.
JA: When you develop a program, what you have to do is to specify the kind of applications that you are interested in. So you set some general guidelines or general parameters, and then solicit grant applications in that area through what is called a request for applications. We also have a program called a cooperative agreement program in which extramural program staff is working as intramural program staff with investigators in the field. And then if you want something very specific, such as you want to have better diagnostic criteria, you can put out a contract that spells out the terms of what you want. What we are interested in doing is trying to find emerging areas, or areas that have been under researched, and stimulate research in those areas. Sometimes that is done by soliciting applications for a cooperative agreement or research grants, and sometimes by working with colleagues in a mentoring program to help them develop interest in a particular area.
LH: A lot of it seems to follow the early philosophy of Jonathon Cole's Psychopharmacology Service Center that identified an area, say, newly admitted schizophrenics, and solicited grants for their study in that

area, and then later identified another area, say depression, and so on. What are the newer programs of interest now?

JA: I think probably the newest development has been the development of the clinical neuroscience centers, which are under Steve Koslow. There has been emphasis on trying to stimulate basic research that is specifically related to disorders such as schizophrenia or depression or anxiety disorder. There has been more funding toward the molecular biology end of the spectrum as opposed to the clinical end of the spectrum. And then, of course, the development of newer generations of drugs has been a startling phenomenon over the past five to seven years.

LH: I had occasion last year to write Steve and ask him for a copy of the wonderful 2nd edition of his book on neurosciences and psychiatry. I was involved in the first edition, but the field has passed me by.

JA: It's a rapidly advancing field. There are techniques that are out there now that neither you nor I learned about in medical school or our training.

LH: Oh, you have to run like hell just to keep up with the pack these days. It is not easy. Well, do you think the federal government, especially the Institutes of Mental Health and Drug Abuse, will continue in the future to try to identify areas of needed research and stimulate them by the mechanisms that you have described?

JA: Yes, I think that is absolutely essential. Even though grant money has gotten a lot tighter in recent years, I think there are numerous fields in which knowledge still needs to be developed. We don't have any perfect treatment for any disorder at this point in time. I think as long as we are dealing with disorders and we don't have ways of preventing them and we don't have perfect treatments for them, there is going to be continuing need for research. I also think that the basic research arena, which is just burgeoning with new knowledge, is going to change the face of modern psychiatry in the next 5 to 10 years.

LH: The genetics of many disorders has been a very difficult area.

JA: It has and continues to be.

LH: I have come to the conclusion that no two of us, even of clones or twins, identical twins, are alike, and especially in our brains. Every one of us has a unique brain, and that may explain the complexity of trying to tie down genetics or specific genes to mental disorders. But, again, that's just a hunch.

JA: Well, I think one of the things that we do know is that all of us process information differently.

LH: Yes.

JA: And even if we are looking at the same phenomenon and we have had the same amount of training, we are going to see it a little bit differently. Even in identical brains you are going to have slightly different processing, and when you process input differently it changes your behavior. It changes how you react to those things. So, it is a very complex area.

LH: The old story of witnesses of the same event coming up with different versions.

JA: Right.

LH: Sometimes it has occurred to me that although the programmatic emphases of the Institutes have generally been pretty timely, the grant structure is set up so that you have to come in with something that almost is certain to be proved, and that's not the way to get really new knowledge. I would sometimes prefer seeing much smaller grants, but many more that were given to people whose ideas were crazy, but have got enough logic behind them and the necessary ways to test them that you could get an answer. What do you think of that approach?

JA: I think you are quite correct, that there is always a tension between innovative or, as you put it, sort of cutting edge crazy kind of research, and incremental research where you go from one incremental step to another incremental step. I think what has happened as grant money has become more scarce, you've seen people wanting to fund more safe research where we can make incremental gains. I think that, from my own perspective, you really need to have a small amount of money set aside just to fund people who have really new and innovative ideas that may have, you know, some rational basis behind them, but don't have the pile of data or the research to back them up. I think we sometimes miss a lot of things by funding incremental research only. That's sort of like the story of the drunk who lost his car keys. He's wandering around under the street lamp looking for his car keys, and they're saying, "Well, why are you just wandering around under the street lamp?" And he says, "Because that's where the light is." I think research is like that. A lot of times peer review committees want to look where the light is, or at best around the edges of that light, rather than going off into the dark and looking for the keys.

LH: In fact, you are almost naive to come in with a new grant proposal without at least some preliminary work that shows it's feasible and there might be some promise to it, which almost makes it a fait accompli when you do the research.

JA: Right.

LH: Well, are you planning to continue your career in mental health administration?

JA: For awhile, yes. I've got a few years left before I want to retire. And right now I'm working with a program that oversees drug testing.

LH: For what?

JA: For 120 federal agencies, and we are developing and evaluating new testing technology, and that's kind of exciting. It's one of the few places in the federal government where you can actually take research and turn it into public policy in a matter of months.

LH: Well, that is unusual. Yes, indeed. Is this regarding drug abuse?

JA: Right, regarding drugs of abuse.

LH: So, what do you think of the war on drugs? Are we seeing the light at the end of the tunnel?

JA: I think we are with the war on drugs, like we are with any epidemic. Right now the epidemic is winning, and it's going to take awhile before we can get it turned around in this country. It's much like we were in the early days with mental illness. We have even less effective treatments for drug abuse in this country, and I think until we can develop better ways of treating drug abuse we are going to have an ongoing problem. When you talk about biological processes and social processes interacting, I think, drug abuse is a prime example of that. What starts out as a sociological or behavioral phenomenon very rapidly turns into a biological or addictive phenomenon, and I think we have a lot to learn about that process and how to treat it.

LH: And it takes about a generation to change habits. I remember in the early 1960s I had a young fellow working in my lab who had been on the track team at the University of Oregon, and he used to do a lot of running. And people would see him running, and they would make the kind of motion, like he was crazy. And now, of course, you see runners all over the place, and people who don't run almost have to feel embarrassed because they are not part of it. I think that came about after President Kennedy had a President's Council on Physical Fitness that gave some cache to doing this sort of thing. So it takes awhile to change what is in and what's out.

JA: I think one of the things that we are seeing now is that, at least in a number of areas, drug use is beginning to be an out phenomenon that it is not socially acceptable, and I think that is a phenomenon that we have to promote.

LH: Well, it has been most successful, I guess, with nicotine addiction. I predicted many years ago that the best way to go about it would be if it is made socially unacceptable by putting on pressures. The pressure has now been graduated to limiting spaces for smoking, looking down on smokers, ridiculing them, making them feel sort of ostracized. In my

house, anyone who wants to smoke has to go outside to the deck and smoke there, but not in the house. So I guess social persuasion is the way to go.

JA: I think that can be very effective, but I also think you have to sort of inoculate each new generation that it's unacceptable. We are now seeing that the junior high school kids are starting to smoke again, and it has become acceptable in that population. So you have to go and work in that population to make it socially unacceptable again.

LH: Well I think the administration's effort to curb the promotion of smoking among young people is very laudable, and I hope it's successful.

JA: Yes, I think that nicotine is a perfect example of where the science has been known for years, and yet it took decades to get that science put into public policy.

LH: It is very discouraging to hear a very prominent politician denying that nicotine is addictive.

JA: It's discouraging to hear tobacco-company executives to deny it too.

LH: And, of course, there are a lot of senators from your area who still think that it is not addictive. We still have a long way to go in educating the public.

JA: Yes, we do.

LH: In looking over the entire field of drugs of abuse, everybody says that treatment is the way to go, and I think there is a lot to commend treatment over interdiction, but the evidence for the effectiveness of treatment, if you take away the effect of methadone and those kinds of treatments, isn't all that persuasive really.

JA: It's gotten better in recent years. There are three studies out now. One in Minnesota, one in California, and a national study called the National Treatment Improvement Evaluation Study (NTIES), which show that regardless of what form of treatment you administer that all of them can be effective in reducing the amount of drugs used, reducing the use of the primary drug, getting people back into employment, and reducing the social consequences of crime associated with drug use. I think we will see more of that kind of data emerge as new treatment studies come about. I think the area that we are the weakest in is the area of prevention for substance abuse.

LH: Well that gets back to the social change that we were talking about.

JA: Right.

LH: Well, the recent study though on the MATCH program, for instance, wasn't very satisfying.

JA: No.

LH: If we use the right program for the right person we should expect to get a good result.

JA: I think, again, that's a problem. It reminds me of where we were back in the late 1960s and early '70s when we were looking at findings with psychological treatment for depressive or anxiety disorders. What we found was that the nonspecific factors of psychotherapy tended to be the most predictive of outcome and that if you tried and individualized the therapies and took out all the nonspecific stuff, you got less effect. I think we are in the same place with substance abuse. These days it's the nonspecific things that you do in therapy that tend to be the most effective.

LH: Just like making a suit of clothes. You have to tailor the measurements to the individual.

JA: That's correct.

LH: Well, do you have anything you want to predict about the future of psychopharmacology from your own point of view as overseeing the broad picture.

JA: I've long since given up my crystal ball about predicting what's going to happen in the future, but I do see some very encouraging signs. I think that some of the newer molecular biology techniques are going to lead to newer drugs that are going to be much more specific in terms of their therapeutic actions and much less problematic in terms of side effects. I think that will be a real step forward in the field.

LH: We may be getting drugs that affect more basic mechanisms than the current ones do. Well, there's hope. I think, say 35 years ago when I began in this area, we all hoped we'd be further along than we are now, and yet by the same token, we haven't done too badly. I've got a project in mind to compare the advances in treatment of hypertension, say, versus treatment in mental disorders.

JA: Oh, I think mental disorders are hands down ahead of that.

LH: You think so?

JA: I really do.

LH: Well, I don't know. I think it's a fairly even match. But, of course, hypertension is so ridiculously simple compared with mental disorders in terms of how to diagnose it and how to explain the pathogenesis. What actually prompted me to think of such a project was that in the early 1950s one of the foundations put out a book called America's Health in Mid Century, and they identified a dozen problems one of which was schizophrenia and one was hypertension. And I thought it might be a good exercise to see where we are by trying to compare

the progress in these areas. We have made a fair amount of progress, I think, comparable to other areas of medicine.

JA: I think if you look at the number of clinical trials and the number of new medications that have been developed, and if you look at the amount of research that has been done to understand the basic underpinnings, then I think mental health comes out way ahead.

LH: Well, I'm glad to hear that. That's a really encouraging note. Well, thank you very much for giving us your viewpoint on where we have been, where we are going, and how to get there.

JA: It's been a pleasure. Thanks.

THOMAS A. BAN

Interviewed by Leo E. Hollister
San Juan, Puer to Rico, December 9, 1996

LH: It's Monday, December 9, 1996, and we're at the annual meeting of the American College of Neuropsychopharmacology in San Juan. I am Leo Hollister and today I am going to be interviewing an old hand in this field, Tom Ban.* Tom, welcome to San Juan for the umpteenth time and we have the great pleasure to talk with you. You and Tom Detre, I think, are the ACNP's biggest beneficiaries from Hungary.

TB: Thank you, Leo.

LH: After the uprising or whatever it was, in 1957, you both immigrated and both wound up in the ACNP. Were you a full pledged psychiatrist when you left Hungary or were you just in medical school?

TB: I graduated from medical school in 1954, and had two years of psychiatry before I left.

LH: Oh, you'd had some psychiatric training?

TB: Yes. We didn't have a formal residency training program in Hungary at the time but I was working as a junior physician at the National Institute for Nervous and Mental Diseases in Budapest

LH: I see.

TB: I even had my first exposure, in Hungary to some of the new psychotropic drugs, like chlorpromazine (CPZ), reserpine, etc.

LH: Now, I suppose there were quite a few who left Hungary at that time? They didn't like to live under a communist regime. At least, Hungary is in better shape today than it was then. Now, you came to join Heinz Lehmann in Montreal. Had that been arranged before you arrived to Canada?

TB: No.

LH: Well, then, what made you go to Montreal, of all the places in North America that you could have gone?

TB: After I left Hungary I was working for about two months at the psychiatric clinic of the University of Vienna in the EEG laboratory primarily. I was also involved with some of the patients at the clinic, mainly as an interpreter. While trying to find a place in the world where to go, I wrote to Wilder Penfield, and in my letter I mentioned that as a medical student I had won an award in a competition with my dissertation on post-traumatic epilepsy. It was a real surprise that he answered and

---

* Thomas A Ban was born in Budapest, Hungary in 1929.

an even greater surprise that he generously offered a fellowship in his Institute. . .

LH: Penfield was a giant. The Montreal Neurological Institute at that time was world class.

TB: It was a fantastic place.

LH: So, that's how you got to Montreal and then it was just sort of accidental that you got to work with Heinz Lehmann?

TB: It was not completely accidental. After my arrival to Canada in January 1957 I spent six months at the Montreal Neurological Institute (MNI). My assignment was in neuroanatomy but I also participated in the activities of Herbert Jasper's neurophysiology division, and attended the epilepsy and multiple sclerosis clinics.

LH: Did you have any contact with Penfield?

TB: I had some contact with Penfield but it was Francis McNaughton who took me under his wings. Then, I did a rotating internship at the Victoria General Hospital of Dalhousie University in Halifax. I spent two moths from that year at St. Joseph's Hospital in Glace Bay, Cape Breton Island delivering babies, before returning to Montreal.

LH: How did this happen?

TB: During my internship I applied to the residency-training program in psychiatry at McGill.

LH: So that is how you got to work with Heinz.

TB: Yes. I asked on the applications form that my preferential first rotation would be the Verdun Protestant Hospital, one of their training facilities, because I knew that Dr. Lehmann was the clinical director of that hospital. I didn't know him, but I had read one of his papers while still in Hungary, and heard people talking about him while I was at the MNI and also at Dalhousie. I became interested in psychopharmacology very soon after I started at the National Institute.

LH: By using chlorpromazine?

TB: After using chlorpromazine for a couple of months in a limited number of patients I became so enthusiastic about its advantages over the old treatments that I persuaded Dr. Sandor, our service chief, that we start in the Institute a quarterly publication on new developments in neuropsychiatry and especially in pharmacological treatment. So, I was familiar with Lehmann's name already in Hungary from reviewing the literature for our publication

LH: Sure. Well, you made a lucky contact. Actually, you got a mentor right at the top.

TB: Yes, I was very lucky. I met Dr. Lehmann for the first time at the Verdun Protestant Hospital on the 1st of July, 1958. It was the first day of my residency. .

LH: I guess, by that time, Heinz was pretty heavily into research, wasn't he?

TB: Yes, he was. He already got his Lasker award for his contributions to the clinical development of CPZ, about a year before that. And, I think he had just published his paper, the first paper in North America on imipramine.

LH: I think so.

TB: Heinz was very much involved in psychopharmacology and in all kinds of other research in psychiatry in those days and within a month I was working with him on several of his projects. In fact, I started to work with him on the second day of my residency. He was interested in the effects of drugs on biological systems of low complexity at the time and we were studying the effects of prototype drugs like dextroamphetamine, secobarbital, chlorpromazine, prochlorperazine, imipramine, lysergic acid on enzymological, growth and reactivity systems. I worked with urease, firefly lantern extracts, proteus bacteria, oat seedlings, the feeding reflex of hydra and dandelion sleep movements. We were also trying to make mute patients speak by inducing fever, giving ECT and administering them amobarbital, dextroamphetamine, chlorpromazine, LSD, etc.

LH: Now, how long were you in Montreal?

TB: About nineteen years.

LH: Nineteen years. Of course, during that time, you become more and more an independent investigator.

TB: Yes, but all those years Heinz and I worked very closely together. The first independent line of research I conducted was in conditioning. It was supported from a grant I received from the Medical Research Council of Canada. But, actually, I got involved even in that area of research on Heinz's initiative. At the time to get our diploma in psychiatry at McGill we had to write a thesis and I got involved in research in conditioning because the hospital had a conditioning laboratory and Jim Prescott, the psychologist who set up that laboratory was leaving.

LH: So, it was the laboratory that dictated your career.

TB: Yes and essentially that Heinz, was looking for someone who might be interested to do research with him in the conditioning laboratory.

LH: He had done a lot of such work before he got into chlorpromazine.

TB: That's right. He had done a lot of research with psychometric performance tests, and, also, some research in psychophysiology. For my

thesis I had to review the literature on classical conditioning and had to do also some laboratory research in conditioning in human.

LH: When did you finish your training?

TB: I received my diploma in psychiatry from McGill in 1960. My thesis, Conditioning and Psychiatry, was published with some minor modifications as a monograph, first in 1964 by Aldine in Chicago, than in 1966 by Unwin in London. The foreword to the book was written by Horsley Gantt, at the time one of the last living disciples of Pavlov. During the 1960s my research in conditioning and in psychopharmacology was closely linked.

LH: So, this is how you got involved in conditioning research.

TB: My objective was to develop a common language for mental pathology and psychotropic drug action, using conditioned reflex variables. . To bridge the gap between pharmacodynamics and psychopathology, we developed a conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. I perceived conditioned reflex variables as functioning patterns of the central nervous system and described mental pathology and the action of psychotropic drugs in terms of the presence or absence of these variables, such as the startle response, extinction of the orienting reflex, acquisition and extinction of the conditional reflex, delayed and trace reflex formation, and so on. One of our papers on the development and use of the battery won the Canadian Psychiatric Association's McNeil Award in 1969.

LH: So, your first line of inquiry was in classical conditioning.

TB: Yes, but I combined some of our research in conditioning and psychopharmacology. We had some interesting findings in those studies.

LH: For example?

TB: For example, findings in one of our studies indicated that changes in orienting reflex behavior was more closely linked to a favorable response to neuroleptics in schizophrenia than the appearance of fine tremor in the hands.

LH: Well, I know you've been one of the few people in our world, who has tried to develop new tests based on classical conditioning for identifying biologically homogenous diagnostic populations in psychiatry. Are you very happy with the present state of affairs in psychiatric diagnosis?

TB: Well, I think, at least in the past 15 years or so we are trying to develop a common language for diagnosing patients.

LH: At least, we are defining our terms.

TB: We have at least diagnostic categories that can be reliably identified. Consensus based diagnoses undoubtedly are an important step forward in the provision of psychiatric service. They might also be useful

in epidemiological research. The problem is that they are detrimental for progress in nosological research. They cover up their component diagnoses that might be selectively affected by psychotropic drugs. It seems the use of consensus-based diagnoses has not provided the necessary feedback for developing clinically more selective and thereby more effective psychotropic drugs.

LH: Well, I think it is a step forward to have this common language and that we all have definitions for diagnoses, but I sometimes wonder whether it might not get in our way because it lumps all kinds of people together and labeled for example as schizophrenic.

TB: The diagnostic concept of dementia praecox or schizophrenia, as you know, was created by Kraepelin by pooling together three major diagnostic categories of illness, hebephrenia, catatonia and dementia paranoides on the basis of their course and outcome. From the time of its inception the diagnostic concept of schizophrenia has been challenged. Karl Kleist in the 1920s divided schizophrenia into two classes of disease, and his disciple Karl Leonhard divided it into two classes with three forms and several sub-forms in each. In the 1980s I had a grant from NIMH at Vanderbilt, to study chronic schizophrenia. And in this study we showed that each form and sub-form of the two classes of disease Leonhard described exist. In fact there were no major changes in the distribution of the different forms and sub-forms of disease in Christian Astrup's patient cohort in the 1950s in Oslo, from Leonhard's patient cohort in the 1930s in Berlin, and in our patient cohort in the 1980s in Nashville.

LH: That's telling evidence that there must be something real about them. How about the stability of the diagnoses?

TB: We developed two diagnostic instruments and with both we could reliably identify each form and sub-form of disease in Leonhard's classification, but we didn't study the stability of the diagnoses. Clinically, patients who are diagnosed with one or another of the sub-forms of the continuous forms of the disease, referred to as systematic schizophrenias, seem to display constantly the same syndrome whereas patients diagnosed with one or another sub-form of the episodic forms of the disease, referred to as unsystematic or non-systematic schizophrenias are more difficult to diagnose when in partial remission. But in relapse they seem to display the same syndrome as in their prior episodes. The same applies to unipolar depression, a class of disease in Leonhard classification that is also divided into two categories of disease, pure melancholia and pure depressions. These are episodic diseases and arguably patients are symptom free, between episodes.

But it seems that in repeated episodes patients are diagnosed with the same subform.

LH: Well, that's true in individuals. Well, how about the concept of spectrum disorders, like depressive spectrum or schizophrenia spectrum diseases?

TB: The concept of spectrum disease implies a relationship between diseases. It is a broadening of a pharmacologically and genetically already broad, heterogeneous category of disease. We need narrower, biologically more homogenous populations for neuropsychopharmacological research.

LH: What do you think about diagnoses like dysthymia? They surely are depressed but they don't meet the criteria of a full-blown major depression. Does that make any sense to you to have these kinds of diagnoses?

TB: Patients diagnosed with dysthymia have depressive personalities displayed by all kinds of depressive symptoms. They don't have a depressive disease in which the mood transforms their experiences.

LH: Let me ask you a question. How much of what we see in these diseases is organic, biological, and how much is functional, the result of interaction with the environment?

TB: In spite of my research in conditioning and my interest in learning theory I look at the different forms and sub-forms of schizophrenia as natural forms of disease in which the interaction with environment plays little role. But, then if you look at the disorders in the DSM-IV, many of those disorders are probably the result of an interaction between nature and nurture.

LH: Well, I think everybody will agree on that it's not just all in our genes. Let me throw another curve at you. How about this issue of co-morbidity? Not only do we have a problem with spectrums, but, we now have an increasing problem of co-morbidity. When you speak of depression, you are often speaking of two or three other things, as well, aren't you?

TB: If you want to get a psychotropic drug prescribed to the widest possible population in which patients have a better chance to respond than to an inactive placebo, the concept of co-morbidity is very useful. For neuropsychopharmacological research, in which progress depends on the identification of treatment responsive forms of illness both concepts are counterproductive.

LH: Since we are talking about psychopharmacology and diagnosis, what do you think of Don Klein's idea that you can establish new entities based on the reaction of patients to a particular drug or drugs.

TB: Well, obviously a diagnostic system based on responsiveness to drugs is desirable. A good starting point would be the identification of treatment responsive forms of illness within the currently used diagnoses. Research in this area must be based on an understanding that responsiveness to the same drug depends to a great extent from the underlying condition.

LH: Your career then in Montreal was in neurophysiology and drugs?

TB: I would say I was primarily doing research in psychopharmacology and conditioning in this order. My primary job was directing the activities of our Early Clinical Drug Evaluation program as Dr. Lehmann's co-principal investigator of a grant from the NIMH.

LH: That's right. You were part of the ECDEU network.

TB: Yes, we were one the first grantees and we were there from the very beginning. After the completion of my thesis I had a research grant as I mentioned before, from the Medical Research Council of Canada to pursue my research in conditioning. But, most of my research in conditioning was closely linked to my research in psychopharmacology.

LH: I see. So, your primary activity was directing the ECDEU

TB: I spent part of my time for a few years on Ewen Cameron's team, who was the chairman of the department in the late 1950s and early '60s. I was responsible for recording psychophysiological measures after the administration of psychotomimetics, like LSD or psilocybin to our patients. Actually, I got on Cameron's team because he needed someone with some experience in conditioning and with psychotomimetics. My first research project in psychopharmacology, and this was back in 1958, was with phencyclidine, a substance originally developed for general anesthesia, that turned out to be a psychotomimetic.

LH: So, you worked with Heinz Lehmann and also with Ewen Cameron while at McGill. Did you work with anyone else while there?

TB: I also worked with V.A. Kral in an NIMH funded psychogeriatric program in which we studied the effects of psychotropic drugs in the aged.

LH: Now, in your work with the ECDEU I suppose you looked at the same drugs as the others in the network.

TB: I think we worked with all the psychotropic drugs during the 1960-s and early '70s in Canada and the United States which were available for clinical investigations. . Bill Guy, who at the time was with the Biometric Laboratory at George Washington University told me that they processed more-studies from our unit than from several of the other units together. We were among the first in North America to study several of the thioxanthene and butyrophenone preparations. And, with drugs that showed clinical promise we conducted a series of investigations. We

also discussed the findings of these studies at symposia organized by the Quebec Psychopharmacological Research Association. We were especially interested in the differential therapeutic profile of drugs. So in one of our studies we compared chlorpromazine, chlorprothixene and haloperidol in the treatment of acute schizophrenia.

LH: That's an interesting comparison. In the company brochure, chlorprothixene was supposed to be good for everything, but it turned out not to be good for very much.

TB: In our study it was comparable to chlorpromazine in acute schizophrenia.

LH: Well, I don't doubt that chlorprothixene was an active drug, but it never went anywhere, you know, never caught on.

TB: We also worked with drugs that didn't catch on in the United States. One of them was methotrimeprazine, Nozinan, and another one was prochlorperazine, Stemetil. They were marketed as antipsychotics in Canada but not in the USA.

LH: I think that decision, though, was probably commercial. At the time SKF had trifluoperazine and they didn't want another piperazine-phenothiazine to compete with it. So, they developed prochlorperazine as an antiemetic rather than as an antipsychotic, but it's a perfectly good antipsychotic.

TB: Then, we also worked with drugs like trimipramine that was marketed in Canada in the early 1960s and in the United Sates in the late 1970s.

LH: I think the drug that most of us ignored or didn't pay much attention to at the time which ultimately, became very important was lithium.

TB: Yes. It happened that I used it first in Hungary in 1955 or '56 at the National Institute and I remember we had to get lithium prepared by the pharmacist of the Institute.

LH: The pharmacist had to make it.

TB: Yes. It was not available commercially. We had a couple of patients on it.

LH: It's surprising that you were able to work with lithium so early in Hungary when lithium was discovered in an English speaking country. You would have thought that it would have more impact in Britain or the U.S. rather than it had in Hungary?

TB: Dr. Sandor, my service chief and mentor, was fluent in many languages and he probably read the papers of Schou or Treutner. And he was interested in trying in his patients everything he learned about. We even managed to monitor blood levels. We tried every possible new treatment he ever read about and we were able to put our hands on.

LH: Those were the good old days when you didn't have to go through six committees and have a waiting time of eight months before you could do a study.

TB: We actually did not conduct clinical studies with any drug; we just used them on the ward trying to help patients. I started to work at the Institute just a few months before chlorpromazine became available. So, I'm probably one of the few survivors who saw how things were before the introduction of the new psychotropic drugs. We didn't have chlorpromazine readily accessible for several months even after we saw how well it worked. We used it first only in some privileged patients who were able to get it sent by their relatives living outside the Iron Curtain. I remember using Largactil from France in one patient, Megaphen from Switzerland in another, and Hibernal from Sweden in a third. I also remember the first patient I treated with chlorpromazine. He was an involutional melancholic. He was agitated, depressed, delusional and theatrical as most patients with involutional melancholia were in the old days when admitted to hospital. Our plan was to treat him with ECT when his family got Largactil from one of their relatives in France. He responded promptly to the drug. We were impressed. My second patient was a negativistic catatonic schizophrenic whom I had to tube feed and catheterize daily for several months. It was a kind of miracle to see him revived, walking and talking and taking care of himself. In both of these patients we used very small doses compared with current standards, about 25 mg intramuscularly three or four times a day. We knew that we must be prepared for blood pressure drop, orthostatic hypotension. So, after the injection I stayed with these patients and took their blood pressure every half an hour or so.

LH: In our original studies, we also gave relatively small doses. I am curious what would happen if we would go back to those small doses.

TB: It would be interesting to see. I also had some experience on Dr. Sandor's service, with reserpine in schizophrenics and with Hydergine in elderly patients with memory problems. Both these drugs were available in Hungary for clinical use in hypertension in those days. Reserpine, was also frequently prescribed as Serpasil for neurotic patients, probably most often for patients with neurotic depression.

LH: Well, I think the whole history of the early development of psychopharmacology has been full with serendipity. Somebody would make a clinical observation that a substance is good for a particular condition and this was sufficient to try to use it in others with the same or similar conditions.

TB: I agree that serendipity played a major role in the discovery of most of our psychotropic drugs, but after a few month of the publication of my Psychopharmacology in which I attributed the discovery of chlorpromazine to serendipity, I received from Henri Laborit a copy of a book he just published at the time with a dozen of so drugs listed on the blank page of the book in the front with the question below: "All these by serendipity?"

LH: Well, you had nineteen pretty good years in Montreal. Why did you leave?

TB: I accomplished the task of organizing a division of psychopharmacology. It was the first division of psychopharmacology in any psychiatry department in the world. But then, I ran into difficulties in implementing a structural reorganization of the psychiatric service in our hospital in a manner that would use optimally what psychopharmacology could offer. I was also interested in extending the scope of my activities

LH: Was Cameron the chairman of the department all through your stay?

TB: No. Cameron resigned in 1966.

LH: And, then who succeeded?

TB: Bob Cleghorn. It was during his tenure that I was appointed director of the Divison of Psychopharmacology. It was also during his tenure that we became the Canadian National Reference Center for Psychotropic Drugs, part of an International Reference Center Network organized by the Division of Mental Health of the World Health Organization in collaboration with the Psychopharmacology Division of the National Institute of Mental Health of the USA. Then, in 1970 the activities of our Reference Center were extended to education, and, we became WHO's first training center for teachers in psychopharmacology and biological psychiatry in developing countries. We introduced our fellows into the methodology of clinical investigations. During their six to 12 months stay they became familiar with the assessment instruments and rating scales included in Bill Guy's ECDEU Assessment Manual. Most of them participated in at least one of our clinical trials in which the collected data were sent to the Biometric Laboratory Information Processing System that was set up at George Washington University to analyze the data of ECDEU investigators. It was during this period that I began with the translation and adaptation of the AMDP and AGP manuals used in the documentation of changes in treatment in adult and geropsychiatric patients in German speaking countries. In the mid 1970s, Heinz Lehmann succeeded Bob Cleghorn as chairman of the department of psychiatry at Mc Gill. During his tenure the activities of the division were extended to all six hospitals affiliated with the Department. In

1976, at age 65, Heinz retired form the chairmanship. And, in the same year I accepted an offer from Vanderbilt, and moved from Montreal to Nashville.

LH: So, you went to Vanderbilt?

TB: I went to Vanderbilt.

LH: Vanderbilt has always been very strong in clinical pharmacology.

TB: Yes. Now, clinical pharmacology was a division of internal medicine at Vanderbilt that was directed by John Oates. We did our research in clinical psychopharmacology at the Tennessee Neuropsychiatric Institute, part of the department of psychiatry, located on the premises of Central State Hospital. TNI was established from a center grant of NIMH and supported by the Department of Psychiatry and the Division of Mental Health of the State of Tennessee. The late Earl Usdin, Dan Efron and Morrie Lipton played a major role in getting the center grant for establishing the TNI.

LH: Now, who was the chairman of the Department of Psychiatry when you went to Vanderbilt?

TB: Marc Hollender.

LH: He was rather supportive of psychopharmacology, wasn't he?

TB: He was very supportive of my activities but I don't know how supportive he was of my predecessor. Marc was a psychoanalyst, a very well organized, honest man, dedicated to teaching. After my arrival he referred to me for consultation some of his long-term patients in analytic psychotherapy and we became friends after one of his patients with a phobic-anxiety-depersonalization syndrome promptly responded to phenelzine, a monoamine oxidase inhibitor he prescribed on my recommendation. A few months later when the patient developed delayed and retrograde ejaculation we wrote it up and published it. A couple of years after my arrival the director of the outpatient clinic died. It took about a year to find a replacement and during this time I spent three half days a week at the clinic supervising residents, and answering their questions related to the use of psychotropic drugs. The questions the residents asked and my answers to their questions were recorded, and Marc decided to edit and organize the material in a logical sequence. Then we complemented the material by a few additional questions and answers. It became a book with the title of Psychopharmacology in Everyday Practice, published by Karger in 1980. Marc and I were very pleased when we learned that our book was translated from the original English into Japanese and Dutch.

LH: I think that having you two on the same book was quite an achievement.

TB: And he really worked on that book. He kept on editing my answers until they were crystal clear.
LH: So, it wasn't primarily a tag along authorship.
TB: It would have been a very different book if he had not done his part.
LH: What do you think of writing books? I always thought you make more money digging ditches.
TB: You are probably right but I never looked at it like that.
LH: Well, it's not only the money; that's probably the least of it. It's the fact that you hope it will have some influence but even then, you're always dubious about it.
TB: Writing a book forces me to conceptualize the findings in our research and integrate it with the information in the literature. And, that, in itself, I find a rewarding experience. Now, I should add that it takes me a long time to write a book or a review because I keep on conceptualizing and re-conceptualizing my findings until I find the way to express what I would like and be able to communicate it.
LH: That's one of the beauties of writing a book. You can philosophize, or tell anecdotes or things that are more personal. And, I find it rather discouraging that many of the new books are lacking this personal touch. All you've got is a lot of information. It does not make any sense to write a book if the author's personal touch is not there.
TB: I think not only books but also reviews should have the identity, the conceptualization of the reviewer. A good review should be more than a summary of all the papers.
LH: Now, when you went to Vanderbilt there was the beginning of a budding institute there, wasn't there?
TB: The Institute, the Tennessee Neuropsychiatric Institute was founded about ten years before my arrival.
LH: That was when Fridolin Sulser went there?
TB: Yes, Fridolin went there about that time. I think he got to the Institute just a little bit after Jim Dingell.
LH: Now, didn't John Davis spend some time there?
TB: That's correct. John Davis was the first clinical director of TNI. But I think John Davis and Dave Janowsky his close associate arrived considerably later than Dingell and Sulser. And, when John left for Chicago, Dave Janowsky, Eddy Fann and other members of John's team left as well. There was no one there on the clinical side for two or three years before I came.
LH: Did you take John Davis' place?
TB: Yes, I was John's successor. But there was a period of time between John's departure and my arrival during which all the funds of the Institute

were used by the preclinical division. The Institute also had a Center grant which just expired around the time of my arrival. At the time John arrived the Institute was prosperous whereas at the time of my arrival virtually all the money the Institute had was used by the pre-clinical division. There was not enough money there to operate a clinical research service safely.

LH: So, you came there when they ran out of money.

TB: The Center grant expired and it was up for renewal. To be able to present an acceptable research grant proposal I had to organize a clinical unit first.

LH: Could you transfer your ECDEU grant there?

TB: Our ECDEU grant with Dr Lehmann was terminated few years before I left McGill. In fact just about the time I moved to Nashville, ECDEU's Biometric Laboratory was closed, and some of the professional staff of the Laboratory, Bill Guy and David Schaffer joined me at Vanderbilt.

LH: Did the funding for the continuous operation of TNI come from the state or private sources?

TB: It came from three sources: the State of Tennessee, Vanderbilt University and the National Institute of Mental Health.

LH: You were at Vanderbilt when Earl Sutherland was there, weren't you?

TB: He died before I arrived.

LH: So, you never had a chance to know him.

TB: No, I just knew that he got the Nobel Prize.

LH: Now, what was your primary thrust at Vanderbilt in psychopharmacology? Were you continuing to test new drugs?

TB: I continued with clinical investigations and we tested several new drugs but the primary thrust of my research was in developing a methodology that would identify the treatment responsive forms of illness, or subpopulations within the diagnostic categories to psychotropic drugs. Development of a pharmacologically valid psychiatric nosology was central to my research during the past 40 years Since pharmacokinetic factors did not seem to explain why one patient in the same diagnostic category responds whereas the other remains refractory to the same psychotropic drug given in the same dose, as early as in 1969 in the concluding remarks of my Psychopharmacology I noted that the "introduction of therapeutically effective psychotropic drugs focused attention on the pharmacological heterogeneity within the diagnostic categories of mental illness." For some time I believed that biological measures would identify pharmacologically homogenous groups within the diagnostic categories of mental illness but by the mid 1980s it became evident to me that this was not the case and that biological measures

were state dependent epiphenomena of mental illness. I published a paper on this with the title, Prolegomenon to the Clinical Prerequisite: Psychopharmacology and the Classification of Mental Illness

LH: It's in an interesting title.

TB: The paper was an extension of my presentation on Psychopharmacology and the Classification of Mental Illness at a symposium on the 15th CINP Congress that was held in San Juan in 1986, in the same hotel we are now. After my presentation I went to the beach with Corneille Radouco-Thomas, who was at the time the editor-in-chief of Progress in Neuropsychopharmacology and Biological Psychiatry, and in the course of our conversation he told me that he would be interested to publish my presentation in his journal. He even suggested Prolegomenon to the Clinical Prerequisite as a possible title. I thought it was a good suggestion and the paper was published in his journal in 1987. In Prolegomenon, I argue that it's not only unrealistic to expect that biological measures would provide pharmacologically meaningful clinical categories of mental illness in the foreseeable future, but I argue also that we need clinical end-points to render findings with biological measures clinically interpretable.

LH: Now, as someone who has been interested in methodology of studying drugs, are you happy with the way things are today? You know that most of the companies now have in-house help that is able to develop a protocol and also have the statistical help to analyze the results. They usually vend out the writing of the paper to some professional writing group and all the investigators do today is gather data. It seems to me like a very dull way to do business.

TB: This is correct and very unfortunate. But I wouldn't blame the companies for doing that. They are business organizations responsible to their shareholders to generate maximum profit. It is the task of the profession that the new psychotropic drugs are optimally used in individual patients. To meet regulatory requirements companies must demonstrate that their drug is not toxic and is efficacious in treatment in at least one of the consensus-based diagnostic groups of mental illness. By the accepted standards a drug is proven efficacious if it is statistically significantly superior to placebo in two clinical studies in that population. We have been aware for some time that our consensus–based diagnoses are pharmacologically heterogeneous, so, it would have been the task of academic psychiatry to extend clinical drug development with clinical psychopharmacological research to identify the treatment responsive subpopulation to psychotropic drugs. I have been rather frustrated for some time that this is not done at the universities,

and, I just formed a small company with some of my former associates and a few other interested psychiatrists to fill in this gap in clinical drug development. It was just formed. I retired from my professorship from Vanderbilt to be able to dedicate my time in developing the company.

LH: What's the thrust of the new company?

TB: The development of psychotropic drugs in a manner that they can be used selectively. We intended to achieve our objective by developing a methodology for the identification of treatment responsive forms of illness, employ the new methodology in multi-center clinical investigations, and delineate the differential therapeutic profile and indications of psychotropic drugs. We hoped to be able to generate the necessary support from industry, government and foundations to achieve our objectives. .

LH: Do you think our clinical tools are sensitive enough to pick up minor differences in the pharmacological profile of psychotropic drugs.

TB: I don't think that the current methodology of clinical investigations with behavioral rating scales focused on the detection and demonstration of efficacy has the necessary sensitivity. But there are some findings that indicate that the Diagnostic Criteria of Research Budapest-Nashville, we developed at Vanderbilt in collaboration with Bertalan Pethö's group at Semmelweis University, has the necessary sensitivity. The DCR is based in part on Leonhard's classification of endogenous psychoses. As you might know, some 40 years ago Frank Fish had shown that one subpopulation of unsystematic schizophrenia in that classification, affect-laden paraphrenia, responds selectively to phenothiazine neuroleptics. There are also some indications that the Composite Diagnostic Evaluation or CODE System provides the necessary sensitivity for the detection of differences in the pharmacology of psychotropic drugs.

LH: That's an interesting and ambitious undertaking. Let me go on to another facet of your multi-faceted career. I recently picked up a copy of Thirty years of CINP, a book you and Hanns Hippius edited some years back. More recently, of course, I've been going through your History of the CINP that you and Oakley edited together. You've been interested in history for a long while, haven't you?

TB: All through my professional career I have been interested in the conceptual development of disciplines like psychiatry and neuropsychopharmacology. I also enjoy figuring out or reviewing developments that lead to our current state of affairs. It is difficult for me to see how research could contribute to the development of a field if it is not done in a historical context.

LH: It would help to have the historical context to put things in. I'm generating a letter, currently, to the Journal of Psychiatry because they had a letter saying neuroleptic drugs are unpleasant to take. I thought that was common knowledge thirty years ago. And, the problem, it seems to me, is that the indexing systems now that are giving this search of the literature so easily and complete, go back only to about fifteen years. And, it's like there's no history beyond fifteen years ago.

TB: It is very disappointing that we have the capability to review historical development properly with the help of computers and we don't use this capability fully.

LH: Now, you and Oakley, are undertaking a similar task with the ACNP history, is that right?

TB: This is, more or less, the case. It would be more correct to say that we are ready to undertake the task.

LH: Well, I think these kinds of interviews are very good, historically, but I'm still a print man. This project with all the visuals is important but I still would like to see something in written in print.

TB: I'm very glad to hear that, because we would like to see these interviews transcribed and in print as well.

LH: You know, David Healy has been doing something similar to what you are doing but, actually, he is writing up these interviews rather than filming them. And, I found the first volume of his interviews very interesting. But, there are of course several different approaches to presenting a coherent historical account.

TB: We seem to have the necessary information in these interviews to present in print a coherent account on the history of the field. Do you think it would be a worthwhile undertaking?

LH: I think it's a worthwhile undertaking, yes.

TB: We are ready to do it. That's all I can say.

LH: You see the problem is that many organizations start off with no concept that they are going to want, someday, to know what their history was, and so they ignore it for the first decade or two. And, then, all of a sudden, someone says, "Gee whiz, we've got a history!"

TB: As you know we have already put in print the history of the CINP. I think it will be much easier to reconstruct the history of the ACNP because ACNP's record keeping has been much tidier from the beginning. And I have a feeling that probably in the "Oakley era" that began with his election as Secretary/Treasurer in 1979 we will be able to find all the records we need.

LH: You know there's a depository of information that they're setting up with Vanderbilt now. It's fine, but really I don't have any old notes.

I, periodically, cleaned out my files and pitched them. I guess some people are compulsive about keeping things.

TB: I think it is very fortunate that finally we have an archive. It was Oakley who got the necessary funds to start it.

LH: Well, Tom, you've not only been a historical figure but now you're a major historian of both of the large organizations connected with the world of psychopharmacology. And, I certainly wish you well in your venture to put it in a coherent, logical and written form. I think a lot of what comes out of these interviews are personal things, the people you've met along the way and people who have influenced you and so on.

TB: I remember Leo when we first met.

LH: You do?

TB: Yes, I do.

LH: Your memory is better than mine. I've got a few years on you though.

TB: You were already well known in the field. It was in 1960 or '61 at the first ECDEU investigators meeting in Washington, DC. At the time the group was small, we could still sit around a table.

LH: Well, one of the great things from my point of view, of being in this field has been the wonderful people, the right people that you meet along the way, some of whom who become very good friends and others you cherish who follow you. And, I think we live in a wonderful era and we're lucky to be in the field we're in.

TB: Yes, we are very lucky.

LH: Well, there's been a great deal of progress since you and I began and I hope we will be able to see some of the bright future that seems be in the making.

TB: I hope so.

LH: OK, Tom.

TB: Thank you, Leo.

BARRY BLACKWELL

Interviewed by Donald S. Robinson
Boca Raton, Florida, December 10, 2007

DR: This is an interview with Dr. Barry Blackwell* for the American College of Neuropsychopharmacoology. This is December 10, 2007 and I'm Donald Robinson, a member of the ACNP.

BB: I'm Barry Blackwell, also a member of the ACNP.

DR: I wonder if you could tell us where you were born and a little bit about your early life?

BB: I was born in 1934 in Birmingham, England. It's an industrial town in the midlands, somewhat like Pittsburgh. In 1938, my father, who was a regional manager for a large tea company, was promoted to India and took my mother and me with him. We lived in Calcutta and when war with Germany broke out we became stranded. After I contracted amebic dysentery in the pre-antibiotic era my parents evacuated me from the city to a boarding school in the Himalayas within sight of Mount Everest. In 1943 the Japanese had conquered Burma and were within a hundred miles of our home. When they started to bomb the city, women and children returned to England on troop ships at the height of the U-boat war. We survived the torpedoes but arrived just in time for the German V1 and V2 rockets. Once again the cities were unsafe so I was sent to boarding school in rural South England. I was in all male boarding schools from the age of five to eighteen at a time when most of the best teachers were away in the army. So it was an up and down education.

DR: You certainly had a different type of education. I wonder if you'd say a few words about university and medical school.

BB: After I graduated from high school I was drafted into the army during the Korean War but had been accepted for Cambridge University after I completed my military obligation. I served as a "hygiene assistant," a military euphemism for sanitary inspector, and was posted to Salisbury Plain where I rode a motorcycle around Stonehenge and spent my time inspecting cookhouses and latrines on reserve army camps. Afterwards I completed three years at Cambridge and graduated without distinction. My major accomplishments were playing rugby for the university, rowing, I was awarded two oars, and drinking beer.

DR: A good preparation for your field!

BB: Perhaps!

---

* Barry Blackwell was born in Birmingham, England in 1934.

DR: Where did you do your medical school and clinical training?

BB: At that time there was no teaching hospital in Cambridge so I went to Guy's Hospital in London which has the oldest rugby team in the world. After three years I graduated in 1961 and went on to complete rotating internships in emergency medicine, surgery and internal medicine at Guy's.

DR: How about your residency in psychiatry?

BB: After completing six months as a neurology intern I was accepted at the Institute of Psychiatry in South London which consists of the Maudsley and Bethlem Royal hospitals.

DR: When, during your early years in medicine, did you get your first publications?

BB: Although I had an undistinguished undergraduate career I was transformed by contact with patients that unleashed both my energy and curiosity. My first paper was written during my earliest clinical rotation, in emergency medicine. It was titled, "Why Patients Visit an Emergency Room" and was published in the Lancet. This remains an interesting and controversial topic today. On my next rotation, in surgery, I published a case report in the British Journal of Surgery on an unfortunate woman with a lump in the breast that turned out to be a leukemic deposit. She bled to death following surgery. During my rotation in internal medicine I became interested in Munchausen's Syndrome, collected a number of cases and published several articles on the topic, including a man I followed for over five years who was had more than a hundred admissions to hospitals in his "career". During my neurology internship I was awarded the annual research prize for a study on the outcome of barbiturate overdose which was also published.

DR: I notice your milestone paper in the Lancet on the cheese reaction occurred in, if I'm not mistaken, 1963 or 1964?

BB: The first mention of cheese reaction was in a letter to the Lancet that I wrote in January 1963. It was followed in October that year by my article describing twelve cases I had collected in nine months, eight of whom had eaten cheese.

DR: So you published what turned out to be a very important paper when you were still a resident?

BB: This was during my first year as a resident when I was twenty-nine.

DR: Could you talk about that?

BB: While I was doing my neurology internship I worked under a chief resident who had written a letter to the Lancet describing a patient who had suffered a subarachnoid hemorrhage while taking tranylcypromine (Parnate). Every time I admitted a patient with this condition I was

expected to take a drug history. It was never positive for Parnate. But several months after I moved to the Maudsley I was sitting in the dining room at lunchtime and overheard residents at the next table talking about an inpatient who had just suffered a possible subarachnoid hemorrhage. I asked if she was taking tranylcypromine. She was. I went back to the Lancet and found six letters describing the side effect in eighteen months. After I bumped into my family practitioner, and he told me how often he saw this side effect, I wrote another letter suggesting it might be more common and serious than was generally thought. About two weeks later I received a letter from a hospital pharmacist, G.E.F Row, who had read the Lancet in the public library and witnessed two episodes in his wife. He described them and went on to speculate about the cause, providing an astute clinical analysis. Similar attacks had not occurred with either butter or milk and she had eaten cheese again without symptoms. He speculated that the sporadic nature of the side effect might have to do with a variable constituent of cheese, not present in other dairy products. I was amused by the letter, showed it to my fellow residents and dismissed the idea. Not long after, a field representative from the manufacturer of tranylcypromine, Gerald Samuels, paid me a routine visit. He urged me to take the letter seriously because he had heard similar reports. Following Mr. Rowe's suggestion we began to be interested in the protein and amino acid composition of cheese but with no real idea of what we might be looking for. But I did go back to look at the hospital menus for the night that the Maudsley patient had her episode and discovered she had eaten a cheese quiche beforehand. The next step seemed logical and traditional. A fellow resident and I took tranylcypromine for two weeks, bought cheese from the hospital cafeteria, sat down and ate it. Nothing happened.

DR: What kind of cheese was it?

BB: Cheddar.

DR: Really! What happened next?

BB: Just at this moment, when I was beginning to be skeptical again, fate intervened. Throughout my residency I moonlighted in family practice. One weekend I received a call from the husband of a patient who was taking a MAO inhibitor. His wife was having a severe headache and had just eaten a cheese sandwich for supper. I jumped in my car, did a house call, and found she was in the midst of a hypertensive crisis.

DR: What was the treatment for a hypertensive crisis in those days?

BB: Fortunately the blood pressure and the symptoms usually subsided rapidly and no treatment was necessary. Most episodes lasted less than an hour. Later on, when we knew what caused the problem and

people sometimes went to an emergency room, α blocking drugs like phentolamine and chlorpromazine were used.

DR: How many patients have you seen with a hypertensive crisis secondary to a MAO inhibitor?

BB: My original report included twelve cases and by the time I completed my doctoral dissertation I had collected twenty-five. This included a patient in the Lancet article in whom I deliberately induced the reaction with the consent of both the subject and her husband. This could never occur in today's ethical climate and was based on the false premise that since I had failed to produce the reaction in myself perhaps I could do so in a patient. In this case I sat at the patient's bedside for an hour and, again, nothing happened. But after I left the unit a nurse called me back for permission to give the patient "aspirin for a headache". I found her in the midst of a hypertensive crisis. Fate and coincidence continued to play a part. I was working late one evening when the on duty resident had been called me to an inpatient unit to see two women in adjacent beds with sudden severe headaches. I joined him to discover that both were taking a MAO inhibitor and both had just returned from the cafeteria after eating cheese. Each was in the middle of a hypertensive crisis.

DR: Amazing! So what did you do to look into the mechanism?

BB: My notoriety got me promoted from the "B" stream of residents at the Bethlem Hospital in the country to the "A" stream on Professor Sir Aubrey Lewis' unit at the Maudsley Hospital in South London. The Professorial unit was the only one where the residents wore white coats. After several months Sir Aubrey took me aside to ask if I was having psychoanalysis. With the Institute's commitment to scientific and descriptive psychiatry this was considered the kiss of death. Presumably my interest in the psychosocial aspects of the discipline aroused his concern. When I pled not guilty Sir Aubrey suggested I take time out from the residency to obtain scientific training and investigate the cheese reaction. He assigned me to work under Ted Marley, the Institute's psychopharmacologist who had also trained in basic research. Dr. Marley's lab was in an old army Nissan hut on the edge of the hospital grounds; its crowded space lined with cages of cats, rats and baby chicks.

DR: What kind of research did you do?

BB: I learned to pith a rat, to inject homogenized cheese into its duodenum and how to record blood pressure responses on a smoked drum. Later, I received a phone call from a local family practitioner about a patient who experienced hypertensive episodes after consuming "Marmite," a sticky brown substance made from brewer's yeast and is dissolved in water as a warm drink. This also contained large amounts of tyramine.

DR: Did you analyze the content of the various foods?

BB: We collaborated with Dr.Mabbit, a microbiologist at the National Institute for Dairying. He analyzed samples of cheese manufactured in different ways as well as several that had provoked a hypertensive crisis. This revealed the way in which microorganisms in the cheese and other maturation factors converted the protein and amino acids into amines, including tyramine. Tyramine content had little to do with taste, color or smell. We realized that pieces of cheese were like cans of garbage, often identical on the outside but different in their contents.

DR: How about Marmite?

BB: Because Marmite was soluble in water it was easy to assay its tyramine content in a rat. The manufacturer provided us with information about the manufacturing process but was unwilling to support our research. Knowing the tyramine content allowed me to conduct a clinical pharmacology study on Gerald Russell's metabolic unit in a human volunteer treated with phenelzine (Nardil) that had experienced the side effect after drinking Marmite. In a series of experiments we showed that the hypertensive response was related to the dosage, duration of treatment and proximity between the time of medication and ingestion of Marmite. The occurrence and severity of the headache was a function of the size and speed of an increase in blood pressure. Slower and smaller increases were asymptomatic.

DR: After you had explained the mechanism of the side effect what did you do next?

BB: I returned to complete the residency and then joined Professor Michael Shepherd as a research fellow. Over the next year we completed two studies, both published in the Lancet. The first was a conventional double blind early Phase II study of a new antidepressant. Our paper, "A Trial That Failed" detailed the difficulty of recruiting an adequate sample of volunteers to meet the diagnostic inclusion criteria. It was a prescient example of what has become recognized as the predictive unreliability of highly selected samples of research volunteers. Our second study was more controversial because it challenged the original claim, by Baastrup and Schou from Scandinavia, that lithium was a prophylactic treatment in preventing future episodes of bipolar disorder. Our article was titled, "Prophylactic Lithium: Another Therapeutic Myth?" It questioned the validity of the author's data analysis and using the same methodology we were able to show a similar outcome in a sample of patients treated with impramine.

DR: Is it true that the prophylactic value of lithium was a new finding at that time and that present knowledge suggests it was correct?

BB: You are right on both counts. But a distinction should be made between the validity of a clinical claim and the research used to support it. The study was flawed in two respects. The sample included patients who had unipolar depression, not just bipolar disorder, and in a longitudinal study the individuals selected for severity of illness sets the stage for a regression to the mean. This is rather like the claim that eating oatmeal can lower your high cholesterol. In retrospect it is fair to acknowledge that both the papers I wrote with Shepherd were examples of a critical and even nihilistic approach for which the Maudsley was known at the time.

DR: You had done research with several well-known members of the Maudsley faculty and had become a senior resident. What did you do next?

BB: Some might say I committed professional suicide. I had a prolonged identity crisis. Throughout residency I continued to moonlight in family practice, working for a physician who was also a friend and commanding officer of the reserve field ambulance I served with. Unsure of whether I wanted to relinquish the breadth of medicine I joined the practice as junior partner.

DR: That must certainly have raised some eyebrows. What happened then?

BB: Paradoxically it created an unanticipated but unique research opportunity. My contemporary, David Goldberg, was also working with Professor Shepherd to develop an epidemiological survey instrument, the General Health Questionnaire, (GHQ) to detect psychiatric disorders in primary care. David chose our practice in which to validate the instrument and calibrate its sensitivity and specificity. We had both graduated in the same class with identical training. In the study, patients completed the GHQ before they saw me. I had about ten minutes to deal with their mostly physical complaints after which David completed an hour-long psychiatric interview in an adjacent office. Time constraints and a medical focus made me miss, one third of the psychiatric disorders. We published two papers in the British Medical Journal. David was first author on one describing the psychometric properties of the GHQ while I was first author on another detailing the clinical issues and barriers to detecting psychiatric disorders in a medical setting. The GHQ went on to become one of the most widely used instruments in primary care research, translated into many languages and adopted by the World Health Organization. David went on to have a distinguished career, ending as a successor to our mentor Aubrey Lewis and receiving a knighthood for his services to British psychiatry.

DR: Obviously you returned to psychiatry. Why, and how?

BB: Eventually I recognized that I was ready to relinquish the diversity of medicine for the opportunity to know each individual in depth that is unique to psychiatry. I also love collecting and analyzing data and primary care offered little time to do so.

During my year in practice I did publish two other small pieces. One was a case report involving a side effect of tricyclic antidepressants, a word finding difficulty, presumably due to anticholinergic activity, similar to the problem in early dementia. My partner and I also studied one of the new tests for early pregnancy focusing on the social and psychological concerns. By the time I was ready to return to psychiatry chance played a part in creating the opportunity. Another Maudsley contemporary, Trevor Silverstone, who was interested in obesity and appetite suppressant drugs, visited the practice to discuss a successful weight management program I had initiated. He had recently returned form a visit to America consulting with a pharmaceutical company that manufactured diethylproprion (Tenuate). They were recruiting for a director of psychotropic drug research. Was I interested? Within weeks I was flown to Cincinnati, offered a job that quadrupled my income and I accepted it.

DR: How did that change the trajectory of your career?

BB: I began the job in the fall of 1968 at the age of 34. It provided all the resources necessary to learn about America and the pharmaceutical industry. Frank Ayd was a consultant to the company and took me under his wing, introducing me to the ACNP and to leading researchers in the field. We collaborated in convening a meeting of all the leading researchers who had made the original discoveries in psychopharmacology and published their personal stories in our book, “Discoveries in Biological Psychiatry”.

DR: Were you able to continue your own research interests?

BB: Frank and I presented several workshops at ACNP meetings and published two papers together on the scientific and ethical problems with psychotropic drug research in prison volunteers. Working with a colleague in another company we wrote an article about the roles and tasks of an industry physician. I published some Phase I clinical pharmacology on the cardiovascular effects of tricyclic compounds and on comparisons of the anticholinergic properties of different compounds using a technique to measure salivary flow.

DR: After two years in the industry you returned to academia. Was it full time?

BB: My job originally allowed me to spend one day a week teaching at the University. Eventually I switched roles, went full time in academia but

continued to consult with the pharmaceutical company. It was a good time to do so because Al Sjoerdsma had joined the company as Vice President for Research.

DR: We share that experience in common. Al was my mentor at the NIH. When I joined his laboratory he suggested I continue my earlier hematology research by investigating whether monoamine oxidase was present in blood. I worked for him for two years and found him a very interesting person. What was your role when you returned to academia?

BB: I was an Associate Professor in both Psychiatry and Pharmacology. In Psychiatry it was a particularly interesting time because the discipline was so different in America compared to Britain. Psychoanalysis was dominant in the US, and the US-UK cross-cultural project had exposed significant differences in diagnostic practices. This was also at a time when graduating medical students could go straight into a psychiatric residency without any medical internship. Many of them immediately began their psychoanalysis with a faculty member. Margaret Mead, who was visiting professor, objected strongly to this neglect of medical training. Fortunately the Chair of the Department, Maury Levine, had written a book on Psychiatry and Family Practice and recognized the need for a psychopharmacologist. Among my duties I took over the psychosomatic unit originally started by George Engel. My future wife, Kathie Eilers, was the head nurse! Together with two creative psychologists, Susan Wooley and Bill Whitehead, we developed a novel cognitive-behavioral approach to psychosomatic disorders. Primary and secondary gain became avoidance learning and positive reinforcement. Rather than assigning a specific personality to each medical disorder we conceptualized a generic “illness behavior” model. This generated a number of significant papers and provoked conflict at Grand Rounds with admonitions from analysts that residents avoid a rotation on our unit, advice which the brightest and best ignored. I continued to pursue interests in psychopharmacology. Wearing both an academic and industry hat I carried out a nation wide survey of attitudes to Phase I research among industrial and academic scientists. Later on I initiated a similar survey on Phase IV, post marketing research. Using prescription data from industry I published an article in JAMA that drew attention to the massive increase in the use of diazepam (Valium) in medical practice. At that time, in 1973, it was routine practice to prescribe the drug to all patients admitted to a psychiatric unit on a “when necessary” (PRN) basis. To study this we developed a “drug seeking index” which revealed differences in use between genders and ethnic groups. It also showed diminished use with time as anxiety declined toward discharge.

The article was published in Archives of General Psychiatry; the first author was a resident working under my supervision, Dan Winstead, now Chair of Psychiatry and Neurology at Tulane University. Whenever possible I tried to involve residents as co-authors and investigators. Two residents at a rehabilitation hospital carried out another study that evolved from my interest in chronic pain and tricyclic antidepressants. In a double blind, placebo controlled study, we evaluated the effects of the antidepressant on both mood and pain. Unfortunately the patients were so eager for attention that the placebo response was too large to show a drug difference. The residents were delighted that empathy trumped chemistry. At this time my interests had begun to broaden, not only into illness behavior, but also patient compliance, both areas where attitudes and beliefs profoundly influence the seeking or taking of psychotropic drugs. One of my first papers on patient compliance was published in the New England Journal of Medicine.

DR: What were your responsibilities in Pharmacology?

BB: I was involved in teaching and research. With other faculty we designed an interesting and unique classroom experiment for second year medical students to demonstrate the placebo response. The students were given one or two, red or blue capsules identified as either a mild sedative or stimulant. All were placebos. Students recorded their own subjective mood states and each others blood pressure and pulse rate. Based on published research we predicted the frequency of outcomes and "side effects" before sealing them in an envelope to be opened in class after the results were tabulated. All the hypotheses were confirmed and the study was published in the Lancet. The Chair of Pharmacology questioned the ethics of the study but the students awarded me their annual golden apple award. Together with other faculty in medicine and pharmacology we completed one of the first studies on the effects of transcendental meditation in hypertension, also published in the Lancet. Because of my interest in tricyclic antidepressants Issy Kolvin asked me to contribute a chapter on the psychopharmacology of nocturnal enuresis in his edited book on the topic. After a re-evaluation of all controlled studies I discovered that the benefit in bed-wetting was almost immediate, consistent with the rapid onset of anti-cholinergic activity, not a delayed anti-depressant response. In this case, psychopharmacology trumped psychodynamic interpretations.

DR: Where did you move to from Cincinnati?

BB: In the mid nineteen seventies there was a surge of 38 new medical schools throughout the United States, including three in Ohio. The intent was to train students in community hospitals and encourage them to

practice primary care in rural areas. With my background in psychiatry, pharmacology and family practice I was attracted to this idea and accepted the Chair of Psychiatry at Wright State University at Dayton in time for the charter class.

DR: How did this influence your teaching and research interests.

BB: It broadened them considerably and elaborated my interest in the biopsychosocial model proposed by George Engel, who was both an internist and psychiatrist. Inevitably the teaching mission shaped my research and writing. For example, I collaborated with faculty in pathology, anatomy and ethics to design a project to humanize the student's first encounter with the cadaver. In a similar vein I worked with a faculty member in the English Department to develop a reading course for first year students using literature that blended humanism with science at the physician-patient interface. Both were published, appropriately, in General Hospital Psychiatry. I collaborated with two pharmacy graduate students in designing a comparative study of counseling versus a pill container in the management of hypertension. Towards the end of my time at Wright State we conducted a national study of medical school curriculum that demonstrated a very significant increase in time devoted to behavioral science.

DR: What were your conclusions about this attempt to change the direction of medical education?

BB: Sad to say, by the time the charter class graduated, it was already clear that the experiment was a failure, for several reasons. Although we tampered with the curriculum, attempts to insert new material were resisted by tradition, time available, and departmental hegemony. Innovation dwindled, as the more creative faculty moved on. The examination of graduates reflected old standards. Student debt dictated a preference for entrance into lucrative, procedure oriented, specialties. Few graduates were drawn to rural medicine sites. My pessimistic conclusions were published as an editorial entitled, "Medical Education and Modest Expectations", in General Hospital Psychiatry.

DR: Where did you move from Wright State?

BB: Further north in the Midwest, in Milwaukee. I was recruited by the University of Wisconsin to be Chair of Psychiatry at its Milwaukee Campus, located at the downtown Jewish Hospital, Mount Sinai. This was a marriage of convenience; the university needed an urban campus to train residents and students while the hospital wanted the prestige of an academic presence to boost its image and revenue. During my recruitment the Dean assured me that the finances for this arrangement, paid for out of the bed rate, were "as good as Fort Knox".

Events proved otherwise. At the time I took over there were five inner city hospitals in Milwaukee. Fifteen years later four had gone bankrupt. Driven by managed care and government mandated inpatient stays (DRGs) revenue declined drastically along with money to pay faculty salaries.

DR: How did this affect your teaching and research productivity?

BB: Early on we managed to cope. I recruited enough faculty to accredit a residency program and sufficient recruits to fill the training slots. With colleagues in medicine I did research on residents' adaptation to their professional role and with neurology faculty I worked in a chronic pain management program and published on this topic. For ten years, from 1977 to 1986, I continued to write the annual chapter on antidepressant side effects for the international publication, Meyler's Side Effects of Drugs. My scholarly interest in compliance continued in collaboration with internists, psychologists and a clinical anthropologist. I developed a major new interest in homelessness and mental illness. This is a population in need of medications but least likely to comply with something so low on their own hierarchy of basic needs. Milwaukee was one of twenty large cities funded by a major grant from the Robert Wood Johnson Foundation. When the project was complete I was invited to write the chapter on psychiatry and mental health services in collaboration with researchers and clinicians from several cities. We summarized ten years of work in the book, "Under the Safety Net". Like many aging academics I now spent more time writing book chapters and less on original research. In 1989 I wrote the chapter on Chronic Pain for the Comprehensive Textbook of Psychiatry and in 1995 contributed the chapter on Patient Compliance for the next edition. In 1990 I was invited to go to the NIMH in Washington DC as director of a task force on Homelessness and Mental Illness. The experience exposed my political naiveté and proved miserable, so I returned home after eight months to rejoin my family.

DR: What did you find back in Milwaukee?

BB: The economic plight of the hospital continued to deteriorate. The multiethnic inner city population it served was either uninsured or enrolled in under-funded government programs. First the hospital merged with another and then was acquired by a large health care corporation run by a new breed of business school administrators whose mottoes were, "no margin, no mission" and "every bucket must carry its own water". Despite a not-for- profit status this meant that every "cost center" must make money to survive. Without income-generating procedures, psychiatry and primary care were least able to do so. As a result I spent

less time teaching and doing research and more time generating revenue, seeing private patients, and consulting to the insurance industry. Eventually the corporation disbanded the psychiatry department. I expressed my feelings in an essay for JAMA's "Piece of my Mind" section which borrowed its title, "No Margin, No Mission". Several years later the academic primary care department met the same fate after faculty were given an ultimatum to quit treating poorly insured patients, resign from academia and become salaried employees of the corporation. The chair of family practice did so, eventually became its CEO, and will retire a millionaire.

DR: Was that the end of your career?

BB: Not quite. After I resigned as chair I worked for two years as the medical director of a small but ethically managed care company. I retained a faculty appointment and published a couple of papers on the influence of case review on care and the role of managed care in medical education. I was unpopular with my colleagues who branded me a "turncoat". My last two papers in 1996 were both on patients with somatization disorders in primary care, and my last book, in 1997, was on "Treatment Compliance and the Therapeutic Alliance". I retired, for the first time, in 1998 at the age of 64.

DR: How would you summarize your research interests over a lifetime?

BB: My curiosity in collecting and analyzing data always arose from what I was doing at the time and not from a single unifying focus. To an extent the cheese reaction came too early in my career and over determined its direction until it became clear that I was too clumsy to be a basic scientist. In Ted Marley's lab I broke innumerable glass syringes, butchered too many rats and smudged countless smoked drums. Eventually my fundamental interest in a biopsychosocial model asserted itself and broadened my horizons beyond psychopharmacology. I collaborated with colleagues, students and residents in many different disciplines on a diverse range of topics.

DR: How did this impact your involvement with the ACNP?

BB: My first contact with the ACNP was when I was invited to present the "cheese" findings while I was still a resident. The cheese reaction and the unraveling of its mechanism are, in many ways, a paradigm of what the ACNP was always intended to be about; the linkage between a clinical outcome and its underlying basic mechanism. Of course this linkage is a lot easier to demonstrate dealing with a peripheral mechanism of action as opposed to the central nervous system and an organ as inaccessible as the brain.

DR: Putting aside that very reasonable caveat do you have any observations about how the ACNP, an organization that intended to link the clinical and basic science interface, has evolved?

BB: Two things strike me as someone who drifted away from the organization as my interests broadened. Firstly, the volume of basic neuroscience in the annual program has increased markedly and the topics have become more remote from clinical findings, even esoteric. The number of clinicians and amount of innovative clinical research seem to have declined. Secondly, the role of clinicians has changed. They are less involved in finding creative new methodology or linkages and almost exclusively involved in interpreting clinical findings within existing paradigms and models.

DR: As someone who has been both an academic and industry researcher can you speculate why and how this has happened?

BB: It begins with acknowledging a distinction between the goals of an industry focused on profit and market share contrasted with the concern of academics and clinicians for accurate information, safety and education. When the ACNP was founded there was a strong mutual interest in discovering new and better drugs and how they affected the central nervous system. The first psychotropic medications were discovered by chance and little was known about mechanisms of action.

DR: In what way has this initial congruence eroded?

BB: From the start industry was more interested in efficacy than side effects for commercial reasons. The Harris-Kefauver amendments requiring that the FDA ensure both safety and efficacy were adopted by Congress at about the time that the cheese article was published in the Lancet. The methodology to do this, the double blind controlled study, was weighted towards proving efficacy, not finding side effects. Only two such efficacy studies are required by the FDA for marketing approval. The size and duration of the study is determined by the statistical power required to show the drug superior to placebo. Such studies encompass small numbers of subjects, treated for a few weeks. Phase I studies usually involved healthy males, closely observed to ensure compliance. Rare or unusual side effects were rarely detected until long after the drug was marketed. Our article, “A Trial that Failed” suggested how rigorous inclusion criteria, based on standard rating scales, can create a procrustean bed that limits the generalizability of findings. Once a drug is generating significant revenue there is a commercial incentive to overlook or downplay side effects.

DR: I imagine the cheese reaction was an example of how a side effect can be overlooked?

BB: Yes, for three reasons. Firstly, headaches are common and occur weekly in about a third of the population. Familiarity breeds contempt. Although the headache due to a sudden large rise in blood pressure has unusual but typical features it is also brief, lasting less than two hours. Physicians rarely got to examine someone quickly enough to make the connection between headache and hypertension. Students are taught that high blood pressure is a "silent" disorder. Secondly, almost everyone eats cheese and even people who experienced a hypertensive crisis ate cheese again without consequences. This led to the natural, but incorrect, conclusion that there was no connection. Pregnancy does not invariably follow intercourse because of the many variables involved but the two are causally related. Our research exposed the variables that intervened between eating cheese and an adverse outcome. Lastly, the side effect had been reported, but not linked to cheese, several years earlier. It was noted in the first study of iproniazid for tuberculosis and again in the first study in depression. Despite these reports, followed by frequent letters to the Lancet neither the FDA nor manufacturer took action. Almost five years and several deaths elapsed between marketing MAO inhibitors and the Lancet article.

DR: I believe this kind of delay in the recognition of a serious side effect is not unusual.

BB: Not at all, for several reasons apart from the inadequacy of double blind trials. Another example would be the more than twenty years between the synthesis and marketing of amphetamine and Phillip Connell's discovery of a paranoid psychosis indistinguishable from schizophrenia. This discovery waited on a method for detecting amphetamine and its metabolites in body fluids. Connell was also a resident at the Maudsley when he made the discovery. Also responsible for the delay is the industry's reluctance to conduct post marketing, Phase IV studies and comparisons between new and established remedies. As the recent CATIE study demonstrated comparison with first generation benchmarks can reveal unexpected findings such as the frequency and severity of metabolic side effects due to second generation drugs. Just as long term follow up of the first generation drugs revealed the risk of tardive dyskinesia.

DR: Did you gather any data on the longer-term use of the MAO inhibitors?

BB: After the cheese reaction was discovered my fellow resident, David Taylor, and I followed up every patient at the Maudsley outpatient clinic prescribed an MAO inhibitor by each of the five consultant psychiatrists. We called this an "operational" evaluation but it may well have been an early effectiveness study. It produced some interesting findings that

were presented to the Royal Society of Medicine and published in the proceedings. The major contribution to good outcome was if a psychiatrist prescribed the MAO inhibitor as a "first choice" drug. This superseded accepted outcome measures, like diagnosis, age, gender etc., and was presumably due to an additive effect of drug activity, placebo response, spontaneous remission and the prescriber's enthusiasm. "Second choice" use was directed to a population that included drug-refractory, side effect sensitive and perhaps less compliant patients. For a while pharmaceutical company representatives capitalized on this effect by paying physicians to prescribe their new drug "to the next few patients that you see." Perhaps an even more important observation, and one we failed to pursue, was made by the psychiatrist who wrote in the chart that "although, this patient never looked depressed before, she looks less depressed now". At the time MAO inhibitors were alleged to benefit "atypical" depression but this term was never fully defined at a clinical and biochemical level. A person who "never looked depressed" would not be included in an early controlled study but might contribute to pharmacological heterogeneity.

DR: Prior to your discovery the cheese reaction was known as "Parnate" headache. Why was this, and how did the manufacturer respond?

BB: Smith, Kline and French developed tranylcypromine. There were two reasons it was singled out. Firstly it was the most widely used MAO inhibitor. This may have been due to the fact that, structurally, it resembles amphetamine and has a mild stimulant effect. Secondly our research showed that it had a narrow therapeutic index compared to other MAO inhibitors. The standard therapeutic dose sufficiently inhibited the enzyme to make the gut permeable to tyramine. As I demonstrated in a clinical pharmacology study that phenelzine (Nardil,) the next most widely used MAO inhibitor, required relatively higher amounts compared to the standard therapeutic dose.

DR: So how did the manufacturer respond?

BB: There were two widely differing reactions. The SKF field representative to the Maudsley, Gerald Samuels, took the pharmacist's letter seriously, mentioned similar reports he had heard about and encouraged me to explore the composition of cheese. The corporate research hierarchy was less enthusiastic. The medical director wrote a letter to the Lancet describing my findings as "unscientific and premature". Some physicians were also skeptical. One patient claimed to have known of the cheese effect but "doctors laughed at the idea". Doubt was eliminated several weeks later when a research team at another London hospital

ate cheese after a MAO inhibitor and demonstrated tyramine spots on the chromatogram of body fluids.

DR: How did the manufacturer respond once the cause was clear?

BB: Ted Marley and I were invited to the company headquarters to discuss our early findings in animals. Their lead pharmacologist had begun similar work and we made a "gentleman's agreement" to share findings and publish them simultaneously. Meanwhile I had begun writing anonymous leading articles and annotations for the Lancet on psychiatric topics. Several months later my editorial contact called to say that SKF had unilaterally submitted their findings for publication. He granted us a few weeks grace to do likewise. Working feverishly, often late at night, we met the deadline and both articles appeared, back to back, in the same issue of the Lancet. Later on Gerald Samuels expressed concerns that his contributions had been overlooked. Together we published a joint article describing his role and he gave me a cheese board engraved with the words, "Everyone eats cheese".

DR: Your story suggests that money, reputation and the quest for priority all played a part in the pharmaceutical company's reactions. Were there other factors?

BB: Another factor that contributes to failure to predict side effects and is generic to many drugs has become more obvious over the years. Manufacturers tend to portray a new product as having unique properties mediated by a single mechanism and involving a specific enzyme, receptor or transmitter system. This provides attractive and simplistic advertising but ignores the fact that enzymes, receptors and transmitters are ubiquitous and multi-functional throughout the body. Biochemists had known for years that monoamine oxidase is widely distributed in tissues, not just the brain, and present in large amounts in the gut where it was speculated it prevented access of amines in food to the blood stream. The original name for monoamine oxidase was "tyramine oxidase", after its first known substrate. Absorption of toxins from the gut and the theory of "intestinal autointoxication" were current from the beginning of the twentieth century when Queen Victoria's surgeon removed her colon for constipation and Bernard Shaw parodied this practice in the "Doctor's Dilemma".

DR: You obviously dug deep into history and the literature to understand and explain this side effect. Are there are other examples of where prescience might have helped predict the cheese reaction?

BB: The personal outcome of my two-year fellowship was a doctoral degree from the pharmacology department at Cambridge University. At first the University declined to accept my dissertation topic because I lacked

resources to carry it out. They relented after Ted Marley intervened on my behalf. Preparation for the degree and the oral inquisition that accompanied it included not only animal and clinical pharmacology but also extensive literature review. Here are a few of the findings. Both tyramine and its amino acid precursor were first isolated from cheese and named after the Greek word for cheese, "tyros". Tyramine was known to raise blood pressure and was used in the first experiments to calibrate the sphygmomanometer in 1911. Tyramine-induced increases in blood pressure were so large and rapid that the experimenter warned of the possibility of cerebral hemorrhage.

DR: You're suggesting that everything necessary to predict the cheese reaction was in the literature prior to its occurrence?

BB: Exactly and this brings us to the second part of your question about the role of the pharmaceutical company. If a young physician with scanty basic science training could uncover the necessary facts why couldn't trained biochemists and pharmacologists anticipate the problem? One answer lies in industry's myopic obsession with specificity which leads to claims that focus on efficacy but neglect collateral actions leading to side effects. Let me relate a personal experience to illustrate this that is eerily reminiscent of the cheese reaction.

DR: Go ahead.

BB: Some years ago my long rugby career exerted its effect on my hip and knee joints. My primary care physician prescribed celecoxib (Celebrex). The mechanism of action is inhibition of prostaglandin synthesis. Colorful magazine and TV ads promised a pain free return to normal activity. Several days after starting treatment I developed an outbreak of erysipelas on my face; the drug is also a sulfonamide. A few days later I became acutely breathless on walking up stairs and went to an emergency room where I was found to have severe hypertension. Until then I was normotensive, but was on the verge of cardiac failure. I reported the side effect to the FDA and the manufacturer who showed minimal interest and asked for no further follow up. The company denied any known effects on blood pressure and sent me selected literature to prove it. Some time later a similar product rofecoxib (Vioxx) was removed from the market and is still the subject of litigation. The current edition of the PDR notes that Celebrex "Can lead to the onset of new hypertension." Like monoamine oxidase; prostaglandins are ubiquitous with multiple mechanisms and sites of action. They can affect not only the joints but also the skin, heart, uterus, clotting mechanisms, blood pressure and gastrointestinal system, sometimes with fatal consequences. How much might have been avoided by more scrupulous

pre-marketing animal and clinical pharmacology or better post marketing surveillance?

DR: That is certainly a compelling story with a striking similarity to the cheese reaction, but without the cheese. Earlier you alluded not only to lessons to be learned from the past but also to more recent events. What are your thoughts on the current state of affairs between clinicians, academics and industry?

BB: The situation is worse for several reasons. Once industry began to advertise directly to the public the market for new drugs expanded dramatically. It encouraged artful and colorful advertising techniques that emphasize alleged specificity and downplay side effects. These are presented in a rapid-fire litany masked by distracting imagery and up beat melodies. Excess industry profits are diverted to lobbying congress into lax legislation and FDA oversight as well as to defending against inevitable litigation. New products continue to be approved after minimal short-term studies with inadequate mandates to perform long term surveillance or effectiveness studies. Often, claims are made for superiority over older generic or standard medications without any comparative studies. Industry has taken virtual control of clinical trials including authorship and property rights over data. Negative findings have been buried in bottom drawers and subtracted from the data base. Overall industry has learned to manipulate the testing and introduction of new compounds to its own financial benefit. It has no incentives to innovate or change the status quo. Can I give you an example?

DR: Go ahead.

BB: Because of my background in both primary care and chronic pain management I was particularly interested in the marketing of duloxetine (Cymbalta) as an antidepressant. Its mechanism is thought to be a dual effect on both norepinephrine and serotonin. This is similar to the older tricyclic compounds and to venlafaxine (Effexor). As we showed over thirty years ago it is difficult to show efficacy in some forms of chronic pain because of a large placebo response. By choosing to study the drug in chronic diabetic neuropathy the manufacturers were able to establish significant pain relief although there was still a substantial placebo response. No attempt was made to compare the product with either tricyclic antidepressants or venlafaxine in pain relief although the former are generic compounds and considerably less expensive. Once approved the product has been heavily marketed and detailed to primary care physicians and chronic pain programs for patients in whom depression is associated with somatic complaints. But this is not the population that was studied. While reviewing the manufacturer's

marketing brochure I noted an early study comparing duloxatine to venlafaxine in depression using the Hamilton scale. The study was listed as a poster but was not published in a peer reviewed journal. The principal investigator was the UK medical director of the pharmaceutical company. The Hamilton scale has an item that measures somatic concerns, including pain. I requested an opportunity to review the data hoping to determine if there was any difference between the two drugs on this item. My request was denied.

DR: I see what you mean. What role do you think clinicians and academic psychiatrists have played in the current state of affairs?

BB: Not a helpful one. Again, money is at the root of the problem. Psychiatrists who carry out clinical studies, sit on FDA advisory committees, are members of editorial boards, consult with industry or follow the lecture circuit and often receive substantial remuneration from industry in one or more roles. A conflict of interest is not neutralized by declaring its existence but by removing its owner from any position of real or potential influence relating to product's safety or efficacy.

DR: That is rather a depressing litany of shortcomings. Do you have any final thoughts to share about either your own contributions to psychopharmacology or the role of the ACNP?

BB: Two, one personal and the other organizational. As someone who has lived long enough to become a "secondary citation," I hope that anyone interested in the scientific and secular implications of the cheese reaction will return to the original sources. The science is published in the British Journal of Psychiatry over forty years ago, in 1967, and the secular story is told in a chapter, "The Process of Discovery" in Discoveries in Biological Psychiatry published by Ayd Medical Communications in 1984.

DR: What are your thoughts concerning the ACNP?

BB: They are almost those of an outsider. I have never participated in the governance of the ACNP and though I am an emeritus fellow have not attended meetings for many years. I believe the ACNP has lost touch with its original mission, not through any intentional actions of its members but because, as an American institution, it is embedded in the ideology of our national culture and politics. America is the only industrialized nation in which health care is treated as a commodity, like cars or clothes. This is costly, inefficient, sometimes ineffective and inaccessible or unavailable for many. Normal market forces and competition fail to control health care costs because people are willing to drive an inexpensive car or wear jeans, but will bankrupt themselves to stifle illness or delay their inevitable death. Secondly, a constitution designed

by refugees from tyranny created a citizenry that shuns government regulation. Today we are living with the consequence of these twin cultural forces. They have resulted in an unbridled profit motive that breeds greed and injustice. It has infected all sectors of our economy: it abbreviated my academic career and has distorted the mission of this organization. On a larger scale civilizations decline when their governments fail to curb the basic instincts inherent in human nature. Psychiatrists should understand this better than most. Psychopharmacologists know there are no pills that elevate empathy or eliminate greed. And if there were, who would take them? The cure for the ACNP and our nation resides in which leaders we elect and how they govern. If the right people are elected the ACNP may have helpful experience and advice to offer in the field of safe, effective and affordable drug development for people with mental illness.

DR: Thank you Doctor Blackwell. That concludes our interview.

CHARLES L. BOWDEN

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 8, 2003

AT: It is December 8, 2003. We are at the 42nd meeting of the ACNP in San Juan, Puerto Rico. My name is Andrea Tone, and we are here today interviewing Charles Bowden.* Thank you for coming.

CB: It is my pleasure.

AT: Why don't we start at the beginning? Why don't you tell us something about your family background, where you were born and raised and your education?

CB: I grew up in a small hill country town in Texas. I lived in Texas most of my life until I completed undergraduate education. I was in a small class that would not be thought of as likely to produce people interested in science, but out of the 50 graduates of this high school class over 40 have now at least a bachelor's degree and about ten have advanced degrees. It was an unusual setting, maybe for reasons of chance rather than anything else. I went to medical school at Baylor, followed by a straight medical internship at Rush Presbyterian-St. Luke's in Chicago. Then, I went to Columbia Presbyterian in New York for residency. It is also important in my career that a national draft program was then in effect for physicians. I served two years in the US Public Health Service at the National Institute of Mental Health Clinical Research Center for Addictive Disorders in Lexington, Kentucky. In fact, I think that Herb Kleber, whom you interviewed yesterday, and a number of other physicians who went on to successful academic careers, had formative, career influencing periods of time spent at that addiction research center, which is no longer in operation.

AT: Let's back up a little bit. At what point did you decide to go to medical school and why?

CB: I matriculated at the University of Texas in Austin as an engineering student and stayed in engineering for a year and a half. I felt that in the field of engineering people were too much removed from other people. There was too much slide rule and dealing with formulas, but not enough human interaction. I thought I could combine science with the desire to impact people's lives directly in medicine. My intent at that time was not at all limited to psychiatry, but was about all of medicine. So, I switched directions in midstream and have never regretted that decision.

---

* Charles L. Bowden was born in Brownwood, Texas in 1938.

AT: How did your family feel when you announced you were going to be a doctor?

CB: I had a grandfather who had been a physician and several uncles who were pharmacists. They were not unhappy with the decision. Later when I switched from an earlier intended direction into internal medicine toward psychiatry, that was a little nonplussing to them. I never had lack of support from them, but some lack of understanding.

AT: What was the perception of psychiatry at that time? Take us back to what being a psychiatrist meant or whether psychiatry was seen with the same luster as say surgery or how did it rank?

CB: It depends on whose eyes one is looking at this through. The eyes that I was looking at it through were those of a medical student. This occurred right at the time when some of the understanding of the ways that the brain chemically controls our emotions was first characterized. Two of my professors, Andrew Schally and Roger Guillemin subsequently won a Nobel Prize for identifying the way in which peptide hormones are transferred from the hypothalamus to the pituitary. Not many medical students have this experience of having people lecturing to them, although no one knew for certain, who seemed pretty clearly to be carrying out Nobel Prize caliber research. Also, to be a medical student within the first two or three years that the first antipsychotic and antidepressant drugs were used, to me, was also very exciting. So the future of psychiatry looked very much the same as that for internal medicine. Certainly, at that time there were many people who were still thinking in terms of lying on a couch as the epitome of psychiatric treatment. I had some analytic training in my career. Almost 40 years later, I still occasionally run into people who will say that they need to be careful of what they say around me lest I interpret and analyze what they are thinking. I have no interest in that nor do more than a small percentage of the psychiatrists in this country. My years in medical school occurred at a time when recognition of the link between the chemistry of the brain and the organization of the brain was, at least for a medical student in the setting I experienced at Baylor, clearly the direction that the field of psychiatry was going to go.

AT: You were at Baylor from 1960 to 1964?

CB: Yes.

AT: And you are saying that the impending rise of biological psychiatry was one of the appeals.

CB: That, and some charismatic professors.

AT: Do you think, and I am jumping forward a little bit here, that neuroscience and the emphasis on biological psychiatry has had something to

do with rehabilitating the field as perhaps more scientific than people thought it was in the 1940s when psychodynamic concepts and the analytical model prevailed?

CB: Oh, without question. Psychodynamic concepts provide a very interesting way of putting together the fact that we have complex ways of coping and interacting. But a weakness of psychodynamic psychology is taking a pinpoint's worth of evidence and expanding into something that explains the world. By contrast, the process of science is taking as much evidence as one can and coming up with as modest but as conclusive a set of results as possible from that large body of evidence.

AT: Tell me more about your exposure to psychiatry in med school before you went on…..

CB: It was pretty standard for the time. There were several professors who had a kind of quantitative focus: measurement and calculation rather than simply interpretation. We had a diverse group of professors, but it included ones involved in the early use of antipsychotics and antidepressants. Even those people who were more analytically trained were influenced by all of this. One person in particular, Howard Crow invested himself fully into teaching medical students. Howard would occasionally buy books for medical students at the medical bookstore. I probably had more exposure to current and historically important writings on psychiatry than most medical students at the time because of working with Howard Crow. I was not the only person. I know at least half a dozen people, whose careers were directed into psychiatry, including the current Chair at Baylor, substantially as a result of Howard's charismatic, total commitment to teaching.

AT: So, you decided to pursue psychiatry about half way through medical school?

CB: Really later than half way through. From four years medical school probably half way through my third year.

AT: Why did you choose Chicago as the place for your internship?

CB: I was elected to membership in Alpha Omega Alpha which is more or less the medical equivalent to a Phi Beta Kappa, and Jim Campbell, the speaker at the banquet for the initiation of members, was the then Chair of Internal Medicine at Presbyterian-Saint Luke's Hospital in Chicago. It was not the only place I applied to. I applied I think also to Baylor, Stanford and not just to Presb-Saint Luke. Dr. Campbell was an extremely impressive individual who had managed to take what had been for a period of time, more or less a top end private practice type hospital, and develop in it into a hospital with one of the strongest internal medicine programs, in part because he put the teaching of

academically oriented physicians at the centerpiece of the entire hospital program and pulled this off in a spectacular fashion. I thought that the best background for psychiatry training was an internal medicine internship. It was just clear to me that the more medicine you knew the better you were going to be positioned in psychiatry. It was going to be hard getting much of that medicine experience in a so-called rotating internship. Now, graduates of medical school go straight into their specialty area training. Then, physicians after their graduation were required to have some sort of a separately constructed internship.

AT: I am struck by what you said about how you felt that internal medicine would be good training for psychiatry. Can you say a little bit more about that?

CB: Well, you are dealing with organs, and the chemical systems that underlie the way these organs function. Whether it is the kidney, liver, heart, or the brain, they have a lot of overlap. As it turns out, most of the medicine that, a person such as Dennis Charney, whom you interviewed yesterday, or I deal with, involves parallel systems in the brain to those, that also provide some of the controls for the heart and blood vessels. So, what one learns about these systems in one area is going to be relevant to another area. If you learn about the autonomic system in relationship to cardiovascular function, a substantial amount of what you learn, not everything, is going to be related to autonomic function of the brain.

AT: OK. So, you went to Chicago, and then you did a residency in New York.

CB: Yes.

AT: Can you say a bit more about that?

CB: I wanted top training, and I wanted it at a most competitive place. I applied to a couple of places in Chicago. I also applied at Harvard, Yale, and Columbia, which has most of the training in the New York State Psychiatric Institute or what still is called PI for short. I think I was influenced toward Columbia because the then Chair at Baylor, Shervert Frazier, came from Columbia, while I was a medical student there. Sherv is a very impressive individual who later headed the NIMH for ADAMHA. He has had substantial influence nationally in terms of research agenda. Just seeing the kind of broadly trained, confident and enthusiastic psychiatrists about the field, as Sherv was, influenced me probably toward what I knew about PI compared to the other places.

AT: What was the specific training?

CB: It was mixed. There was a kind of idiosyncratic psychoanalytic institute still there. But, there was already a large amount, as continues to

this day, of biological research going on as well, and the training was sort of a divide between the two. You went above the ground floor and you were in the research component of the psychiatric institute. You went below and you were dealing with clinical care that was still based more on notions that no matter what the presenting symptoms of the patient were, you would likely give the same diagnosis. This derivative of psychoanalytic thinking, prevalent at the time, emphasized that it was not diagnosis that mattered the most, but rather the process of looking back into what happened to the patient at age two, four, six, or eight. For many years at PI and for that matter across the US patients admitted were diagnosed as schizophrenic much more frequently than would now be the case. Occasionally residents and faculty would refer to such patients as PI Schizophrenics. We sensed that some of these PI Schizophrenic people had either mood or personality disorders.

AT: Why were they all being diagnosed with schizophrenia?

CB: For a period of time in the US, patients with any psychotic features, even if transient and related to drug taking, or to stressors, or bipolar disorder or addictive disorders; tended to have their psychosis equated to schizophrenia.

AT: You mentioned at the beginning of the interview that you ended up going to Lexington and getting some training in substance abuse, addiction, and other things, and I understand from reading your CV that along the way you got married and had children. How did this all fit together? At what point did you get married and have kids and juggle it all?

CB: I met my wife, who's here at this meeting, at the University of Texas at Austin, and we married the year before I matriculated in medical school. She was a mathematics major working in computers. She first worked for Texaco in a room as large as the one we are in now, full of computers and that influenced my going to Lexington in that she decided that, having done systems analysis work for the American Medical Association, then for Mount Sinai Hospital, and for a department store, Bambergers, in New York she wanted to obtain a master's degree in library science. I requested that the Public Health Service assign me some place where she could work on a library science degree. Two facilities met those criteria: one in Fort Worth and one in Lexington. I thought they would probably assign me to Fort Worth since I was from Texas, but they assigned me to the one in Kentucky. She obtained her library science degree and was later the director of the medical school library in San Antonio for a number of years. We have two kids. One was born in Kentucky and one in New York while I was at Columbia. Both daughters ended up going back to Columbia, one as an undergraduate and

one to law school. Thus, our ties to Columbia are substantial. In fact, all of their education was in the northeast at Ivy League schools. They now live in the northeast. Well, one recently moved as a result of her marriage to Nashville. Our older daughter was born when I was a resident and the second was born when I was in required military experience through the NIMH clinical research center in Lexington.

AT: Can you tell us a little bit more about the military training you had?

CB: It was in the Public Health Service. If you are at NIMH, you are essentially in the Public Health Service. This was an addiction research facility. I was there during a period when there was a national civil commitment law in place that allowed persons with heroin addiction who were facing criminal charges the alternative of voluntarily committing themselves to a period of enforced treatment which usually involved methadone. During my residency at Columbia I had worked with Bob Spitzer and Jean Endicott on a research project measuring symptoms using structured rating scales and published with them an article that was applicable to measuring outcomes with methadone. I then published two of the first papers on long-term outcomes with methadone maintenance as a result of work I conducted while in the Public Health Service where I worked with another psychiatrist, Bernard Langenauer who was in the same type of required military commitment that I had. We had a very effective working relationship, putting an academic perspective to the administrative and clinical care that was the expected from the physicians at the Center. That is the way it happened.

AT: Did you want to go to Lexington, or was it just something that was kind of required?

CB: No, I wanted to continue my training. This was during the Vietnam War. I was pleased to be in the Public Health Service because I thought that the US had made a bad decision in terms of the quagmire we got ourselves into with Vietnam. I did not expect it to have any academic component to it. While there I was able to work a day a week at the University of Kentucky's Department of Psychiatry. A professor there, Myron Sandifer, was one of the key investigators in a combined United States and United Kingdom study looking at what we mean by the diagnosis of schizophrenia. In the US, given the same set of symptomatology, a person was about 12 times as likely to be diagnosed as schizophrenic than if he or she expressed the same symptoms in the UK. The study was not the only factor that brought about change in diagnostic practices in the US. There were other factors, such as the development of new psychotropic medications. The study definitely helped move the US more into the mainstream of ways of thinking about descriptive

psychopathology and how to utilize it. A remarkable number of people who later developed research carriers spent early parts of their professional careers at Lexington. George Vaillant conducted outstanding work both while at Lexington, and later at Harvard. Following his military commitment at Lexington, he assumed leadership of a longitudinal life course study of the members of a first year class at Harvard, and some similar studies. He conducted a study of the prospective life course of persons who had become addicted to heroin.

AT: Did the treatment at Lexington in your estimation work and what did it consist of? You mentioned studies that you did, and they were pioneering studies. How did they differ from traditional thinking about treatment at that time?

CB: Well, methadone itself has all the properties of any other opioid, but instead of having a pattern of blood levels and behavioral effects that are a bit like roller coaster, the blood levels of the drug and thus the behavioral effects are largely maintained within a narrow range. So, rather than being incompatible with daily work, methadone was clearly compatible with performing routine functions for a pretty large percentage of people to perform ordinary role responsibilities as spouse, living life independently, working, and things like that. Was the person still addicted to an opioid? Yes. But in a psychosocial sense they were able to function without breaking the law and the like. Is that full recovery? No. But it was maintenance care and clearly superior to a life of heroin addiction with a street type of existence. There was no question that it was a real advance. That is what our research showed.

AT: So, the publications that came out of your experience at Lexington advocated methadone treatment?

CB: I tried not to be an advocate. I just tried to let the evidence determine what conclusions I and my co-authors drew. So, I would not call it advocacy, but the studies were positive. I recall the title of one of the two papers we published. .The title of one was “Methadone Maintenance: Myth and Reality”. That was a catchy title. These studies were published in the American Journal of Psychiatry, so they had some influence.

AT: How did that then change the field? In what ways did they shape large understanding of substance abuse?

CB: I think it shifted it to the notion that we could look at maintaining a person and achieving some successful indices of outcomes without necessarily eliminating the addiction. After completing my two years of duty at the Addiction Research Center at Lexington I continued to work in addictive disorders but eventually segued into mood disorders at the University of Texas Medical School in San Antonio. Methadone

still continues to be used and .in some ways, and I am speculating, it helped to move the field to disassociate total cure from the psychosocial, functional goals. I think the work has some implications for chronic diseases as for example in bipolar disorder. We don't cure bipolar disorder. The person learns to understand something about the bipolar disorder. He or she takes some medications to control the symptoms. We don't cure these diseases. We don't cure heart disease. Maybe we cure bacterial pneumonia. The number of diseases that we cure, unless we move to a sort of post-genomic era, is miniscule.

AT: How did you then move to mood disorders? I see that you have done a lot of work in the area of anxiety and depression.

CB: First, mood disorders overlap addictive disorders. That was clear. There were more opportunities for innovative outcome studies in mood disorders than there were in addictive disorders. It appeared to me that I was going to be more locked into an externally defined approach to treatment that was not going to give me much opportunity for scientific innovation if I stayed solely in the addiction area. So, I started working in anxiety and depression and ended up as a part of this NIMH collaborative study on the psychobiology of depression which has influenced my career, Some of the members of the ACNP were participants in that clinical collaborative study. Some of the most intriguing findings in that study were in regard to the bipolar subjects, even though it only included a small number of bipolar disorder patients. Alan Swann and I each viewed the results in the bipolar patients as remarkable, and worth pursuing in follow up studies. We had strong, significant differences in relationship to treatment outcomes in underlying aminergic and cortisol system abnormalities in the group with bipolar disorders from the group with recurrent major depression. That got me, and Alan on the paths that our careers have subsequently taken.

AT: In 1970, when you were looking at the data and were intrigued by it, what was the thinking about the origins of bipolar disorder? What was your thinking about origins and appropriate treatments, and how did you take this ball and push it in a new direction?

CB: In some ways the thinking was not at all different than it is today, because there were a number of studies that clearly showed that bipolar disorder was highly heritable. No one doubted that. Even if you go back to Hippocrates, the only emotional disorder that he really wrote about, translated from the original Greek was manic depressive illness. He describes it pretty well. Throughout history, and you pick your century 13th, 14th, 15th, 16th, there were physicians writing about bipolar disorder in ways that holds up pretty well today. One difference is that

the early work generally viewed the bipolar group as a very small percentage of the population and that many more people had depression or schizophrenia. For example, only in the last seven or eight years, consequent to some pioneering work led by a child psychiatrist, Barbara Geller, has there been a general understanding that bipolar disorder more often than not is first expressed clinically during adolescence or in earlier childhood. Prior to that anything in kids that involved social or psychological symptoms tended to be attributed to bad parenting or interpreted in a very different fashion from psychiatric disorders in adults. A person I spoke with last night at a social event, Bob Findling at Case Western University in Cleveland, is typical of a new cadre of a dozen or so absolutely top rank investigators working in bipolar disorder in kids these days. . It is difficult work because the younger the kid the less able to tell you what is going on, although retrospectively they come to understand, as the clinicians do, that their problems were manifestations of their bipolar disorder. In all of these subjects we try to determine when they first experienced bipolar disorder, and whether it was treated or not. One patient responded to our questions with a sense of humor but also insight, "I have had this illness since I was a zygote."

AT: How do you tell in a two-year-old or a three-year-old?

CB: You need to talk with a Bob Findling or Barbara Geller rather than me. Interestingly, I think a majority of the child psychiatrists working in this area at the top levels are women. The answer is that it is not easy to decipher. We can't administer a structured rating scale to a two-year-old. Women sometimes describe that they experienced greater activity in utero with their kids who eventually are hyperactive.

AT: You mean lots of kicking?

CB: Yes. The early, specific symptoms involve grandiosity and hypersexuality. I think Barbara Geller's work has been the most influential on this. It is possible to recognize grandiosity, hypersexuality and reduced need for sleep in very young kids. If a first-grade child goes to the principal's office and starts telling the principal how he or she should run the school you probably are dealing with someone who has some grandiosity that is not accountable for by intelligence. That kind of behavior is highly associated with the likelihood of bipolar disorder.

AT: I understand that you have limited time. How much time do you have?

CB: Another eight minutes.

AT: OK.

CB: I am on the program to present soon.

AT: What would you say then your key contribution has been to our understanding about the treatment of bipolar disorder? Weren't you one of

the first to question the efficacy of lithium as the drug of choice for the treatment?

CB: Some would say that I undercut the role of lithium; I don't think that is true. I think that lithium is a very efficacious medicine, and lithium and valproate uniquely share some common neurobiological mechanisms that at least at this point no other treatment used in bipolar disorder has. But lithium is a very poorly tolerated medication. I think the evidence increasingly is that it worsens depression more often than it helps depression. So, it brings the mania down, but it also, in laboratory animals, in human volunteers, and in people with bipolar disorder, worsens sometimes the depressive side of this illness. I hope that my contribution, which is more for others to assess than me, is mainly viewed as recognizing the complexity of the symptomatology of bipolar disorder, its association with some fundamental neurobiology, and the identification of a series of different drugs that expand effective treatments. Expanding options that patients have, leads to better control of this illness and fuller lives than would be possible with lithium alone.

AT: This will be the final question before you have to take off. What are these other options?

CB: I wish I had more time to discuss the story. By the time that clinical research staff with Abbott labs came to me asking about my interest in participating in a study of a form of valproate, Depakote, which they had developed and marketed, I had been working with bipolar disorder for a number of years. Some of the limitations of lithium were understood. Two medications, that had been most often used as alternatives to lithium, both without much in the way of systematic studies having been conducted, were drugs first employed in the treatment of epilepsy. The first was valproate, and the second, shortly thereafter, was carbamazepine. Carbamazepine had somewhat similar long-term adverse effects to those of lithium. Valproate had its own side effects but was generally much more tolerable. It also seemed to have a broader spectrum of efficacy. A regional research liaison person with Abbott came to me and asked if I would be interested in conducting a small study with valproate. I said that I thought the small study would be a mistake and I recommended that they conduct a solid study that would be acceptable to the Food and Drug Administration, because the drug might provide a fundamental new approach to treatment for bipolar disorder. The CNS group at Abbott had recently hired an internist who was working in their neuroscience area. They did not have any psychiatrists in the group because they only viewed valproate as an anti-epileptic drug. This person was excited by my idea and pushed through the protocol that led

to the first large-scale study. Independently –I did not know this at the time– two residents at McLean, Paul Keck and Sue McElroy had recognized the same kind of potential for valproate as I did, and had obtained some research funding from Abbott. The results of the two studies resulted in the FDA's approval in 1995 of divalproex. There is a major element of chance in scientific investigations. It isn't blind chance, but a kind of serendipity seized on by the individual who recognizes an opportunity that other people partially recognize, but not fully.

AT: Final question. Where do you think we are headed in the treatment of bipolar disorder? Fifteen years from now, what do you imagine it will be?

CB: I wish that I could say that there were going to be tremendous breakthroughs. I think that the disease, even though it has strong genetic contributors, is still going to yield only grudgingly to the genomic and post-genomic studies in terms of other treatments. I think my view may not sound so enthusiastic but I think that the medications that we have today will still be the main approach to treatment. They will be combined with educational psychotherapies. I think where the main differences will be is that some of the neurobiological studies will have made their way into diagnosis and factor into selection of treatments. They won't be at a point where you can say well because of a genetic characterization of an eight-year-old, we can prune gene expression and prevent the clinical expression of the disease. I don't think we will be at that point. I think that the changes will be incremental, not epochal and dramatic. I think that we will come to an understanding that bipolar disorder is much more than simply having a high or a low and more a complex mixture of about five different behavioral dimensions. Consequently, a fair number of conditions that have elements of bipolarity will come to have treatment with some of the same strategies, medication and otherwise, that benefit the most easy to characterize bipolar conditions. This is especially going to be true in some anxiety type conditions.

AT: Thank you so much. I am sorry our time has to be cut short. Is there anything you would like to add that I haven't touched on?

CB: Maybe one. One of the things that have been particularly gratifying in working in bipolar disorder is the intellectual and emotional investment in this illness of families and patients with the disorder. Patients come to understand that this is a disease just like any other disease. They want to learn about this illness, and that makes it extremely gratifying. They want, and are able to achieve in many instances, the same kind of productive life that you and I have. I have psychiatrist and physician

colleagues who have bipolar disorder. So, we are dealing with a disorder which peculiarly in its most benign presentation actually confers some competitive advantage on people. They are more energetic. They have more curiosity. They have more in the way of creative ideas before breakfast. Yet, if it is a little bit beyond just that, they are not able to pull those things together. So, they may be highly educated but functioning socio-economically at a level much below that. We have the opportunity not just to keep people from being sick and nonproductive but for contributing to the function of some people who are among the movers and shakers in our society, both in terms of literature and arts and in terms of business and the like.

AT: Thank you so much.

CB: It is a fascinating area.

JONATHAN O. COLE*

Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 11, 1994

LH: It's a pleasure to have you here for this interview on the history of psychopharmacology because I think you are probably one of the oldest historians, not in terms of actual age, but in terms of durations. Of course, you've been part of this wonderful ACNP. Tell me, how did you get started in medicine and psychiatry and psychopharmacology?

JC: My mother had a fixation on a surgeon, in my late adolescence, early, around twelve or so. And, then, she had manic or depressive episodes often, which may have contributed. And, my best friend in boarding school, had a father who was a doctor and somehow or other I ended up in medical school during World War II. And, at Cornell, I got under the influence of Harry Gold, who was doing double-blind studies of angina.

LH: Well, those Cornell conferences on therapy were really landmarks.

JC: Yes. I interned at the Brigham and did my psychiatric residency at Cornell. So, I got exposed to Harold Wolfe's neurology conferences, which were also pretty good. And, then, I went into the army for two years. When I got out I heard the National Academy of Sciences advertised to all the psychiatrists coming out of the service. They were looking for an MD to service about four committees, they had at the academy. I applied and got the job with the help of George Thorne, who was my chief at internship. The National Academy had committees on stress, psychiatry, alcoholism, and drug abuse.

LH: Good for you, you got the job.

JC: Anyway, I got in my job some exposure to research and how committees review research. The committee on psychiatry was supposed to advise the army, on psychiatric research, but the army didn't want any advice. So, we were a committee without a function, as far as I could tell. And, then I went up to NIMH to find out what they were doing about reserpine and chlorpromazine, which just arrived at the time. They had given a grant to Ralph Gerard through the National Academy to organize a conference and I did the legwork for the conference and, eventually, edited a book on the proceedings, called Psychopharmacology Problems in Evaluation. And, then, Mary Lasker and Company dumped two million dollars on NIMH to run a grant program in psychopharmacology.

LH: What year was that?

---

* Jonathan O. Cole was born in Boston, Massachusetts in 1925. Cole died in 2009.

JC: 1956, the same year the conference was held. They couldn't get Joel Elkes or anybody sensible to run it, so they ended up with me, because I'd run a committee. I knew something about research grants and something about committees and was handy and willing to take the job, so I ended up at NIMH running a program at age thirty-one or something like that.

LH: It seems to me I remember a meeting we had where you and Ralph came over and visited with the VA group.

JC: VA was doing a multi-center study and about that time, Nate Kline testified to congress saying that, "by-god, the NIMH should do a multi-center study", and sooner or later I did. It was an interesting time because we were getting money given us faster than we could spend it and could, in fact, do things like multi-center studies, because we had a lot of extra cash.

LH: The Psychopharmacology Service Center had another name, initially.

JC: No, that was the original name until it got changed to the Psychopharmacology Research Branch. I set up a scientific information operation under Lorraine Bouthilet, which, actually, did quite a job until it got expanded into the mental health information system and clearinghouse.

LH: So, you started The Psychopharmacology Service Center. In what year did you?

JC: In 1956 and ran it for eleven years. We, first, did the study in schizophrenia, in acute schizophrenia, comparing placebo with three phenothiazines in nine hospitals and that went quite nicely and produced highly sensible results. And we went on and did a second study without placebo in slightly less acute patients, which came out all right. Then, we did a study in chronic patients with high dose, low dose placebo and, I think, doctors' choice treatments. Bob Prien wrote up most of that. Then, we did a study in depression, which was a bomb. I don't think it was, even, ever noticed.

LH: I once did an antidepressant study that was a bomb.

JC: And, we and Sy Fisher did, some stuff on Librium (chlordiazepoxide,) placebo and what not, in anxiety. The Early Clinical Evaluation Unit (ECDEU) program started about that time. The name was changed to NCDEU and there is still an NCDEU meeting every spring. .

LH: Was the last one about the thirty-third?

JC: Something-like that, yes.

LH: I remember the first one; seems like it wasn't that long ago.

JC: I modeled the ECDEU program, or at least in part, on a program Nathan Eddy was running for problems of drug dependence. The program had

originally twelve or thirteen grantees, but it turned into a meeting where industry and investigators could get together.

LH: It has become quite a big one now.

JC: Actually, it's less selective, but sometimes more fun.

LH: If I recall correctly, all the hospitals in your nine hospital study were non-academic hospitals. Weren't they state hospitals?

JC: No, we had a mix. We had Paine Whitney, Institute of Living, DC General, and the city's psychiatric hospital in St. Louis, whose name I forget now.

LH: Malcolm Bliss.

JC: Malcolm Bliss.

LH: You had one site in Louisville, didn't you?

JC: No, we had one in Lexington, Kentucky, and Rochester, New York, a State Hospital, Manhattan State Hospital and, I think, Springfield State Hospital in Maryland.

LH: In Springbrook?

JC: No, it was in Springfield, actually. That's where Gerard Hogarty came from to the PSC. He was the social work chairman on that project, actually.

LH: So, there were seven of them that were non-academia.

JC: Yes, I think we probably did a little better, with non-academic hospitals. Actually, the two lowest dropout rates were in hospitals where the principal investigator was the superintendent. No one dropped out from placebo. It was interesting. We, actually, had a tenth hospital, Stoney Park or Stoney Lodge, or something like that, up the Hudson, but they couldn't provide the patients, so we dropped them. We just went around at an APA meeting and approached people we thought might be interested and talked with them. We didn't put it out for bid or anything. We just sort of did it. Nobody complained in those days.

LH: Well, that was a landmark study, which allows me to say, I think, that we at the VA got robbed.

JC: We had more credit than the VA did and I think that was probably wrong, but it was nice.

L.H.: Well, between the two of them, certainly, it erased any doubts about the effectiveness of these drugs. There still were times when people weren't really quite ready to accept them. And, it was often cited that a sizeable number of the patients, I think, something about twenty-five percent on placebo, showed improvement.

JC: Yes.

LH: And, that was cited as a tendency to spontaneous remission. Do you think it could possibly be the case that many of these acutely psychotic patients weren't truly schizophrenic?

JC: Well, some of them were, undoubtedly manics, and a few of them may have had amphetamine psychosis. I wouldn't want to guarantee that the twenty-five percent got better actually were not schizophrenics. Some of the current studies, like the Hillside first episode schizophrenia study have lousy outcomes. Anyway, we had really great placebo-drug difference. Then the placebo group did better at two year follow-up than any of the.....

LH: Of course, because they were subsequently treated with drugs. .

JC: We did a two year follow-up and found that there was a lower re-hospitalization rate in the placebo patients than there was in the drug treated patients, for some unknown reason.

LH: The VA had a similar experience. Well, you certainly did a series of landmark studies there and, then, you left the Psychopharmacology Service Center in when?

JC: 1967.

LH: 1967.

JC: Jerry Levine took over and I moved up to Boston to run Boston State Hospital, which in retrospect, I helped to put out of business.

LH: I think there is room for an asylum these days.

JC: People used to come in and say this was one of the best state hospitals in the country and I used to have acute attacks of guilt, doubt and what not.

LH: Well, that was a movement all over the country. I remember in California that Governor Reagan decided to close all the hospitals and, of course, made no provisions for after care.

JC: We did fairly well on after care.

JC: Cooperative apartment programs and things of that sort. We were doing home treatment and other such things.

LH: So, after you ran the Boston State Hospital to non-existence, you went back to academia, did you?

JC: I took a year as chairman at Temple to get out of town. I was beginning to feel that I was doing enough irregular things that one of the old civil servants, who ran the business end of the hospital, was going to get me one of those days, if I kept on doing what I was doing at the hospital. There was no insurance for any of my acts as superintendent. The state would cover me for seventy-five hundred dollars

LH: Good grief.

JC: And, there was no purchasable insurance that would cover one's acts, as superintendent, in those days. For a year, there was a law that covered us and made us unable to be sued but, then, the change in the law lost that section. Anyway, I went to Temple for a year and my, then wife, said, "Try it for a year and if you like it, we'll move". By the end of the year, I'd figured I didn't like Philadelphia and I got offered a job at McLean. And I've been, more or less, there ever since, almost twenty-five years, now.

LH: You've been there a long time.

JC: McLean's, actually, been very nice till lately. The last year a few things have gotten kind of dismal and they were firing people, and doing all kinds of things.

LH: That's because of budget?

JC: Yeah, we turned ourselves inside out to provide multiple levels of care and we were all ready for National Health Service, except that nothing ever happened. Nobody wants to pay for day hospitals and halfway houses and things, unless you have a private insurance.

LH: You'd think the insurance company would grab at it.

JC: They do, to some extent, but you'd better negotiate with them. We've done some business in halfway houses. At one point, we had one hundred and twenty patients in halfway houses. At Boston State that was fine because you had a fixed number of employees. You could get rid of patients, and you could use the people for doing other things, but in private hospitals, these days, if you get rid of patients, you, also, get rid of beds and, then, you get rid of ways of earning money. Everything begins to sink. At the end of the slide, I don't think we're going to go broke, but it's going to be a rough five years.

LH: Now, who is in charge now after Fred resigned?

JC: Steve Marin took it over and is still running it. He now has an office down at Mass General and is looking more and more disinterested in the hospital. I got offered some money for a crummy little residency program, which works with a Catholic hospital in Brighton and I've now moved over there, half-time, teaching. I'm now director of residency training at St. Elizabeth's, like two or three days a week, and give them two days a week at McLean, as a senior consultant or something or other. I can't remember what.

LH: I think McLean always comes out on near the top of the list of psychiatric hospitals. Do you have as many people doing research there as you would a few years back?

JC: More, if anything. I think our research is gradually climbing over time.

LH: Is this due to successful grant applications?

JC: Mainly, grant applications. Sherv Frazier, once he got undepressed over the plagiarism nonsense, has raised something like twelve million dollars in endowments, so, we, even, have some endowment income to draw on. We keep body and soul together. .

LH: So, it's still a major research hospital?

JC: Yes. Research is still going on, reasonably well.

LH: You mentioned Ralph Gerard, earlier. You were sort of his protégé, weren't you?

JC: I guess. I assisted him in organizing the meeting we talked about. But when I got my name first on the book he didn't like that very much. Then, he got a big grant out of me, somehow over my dead body.

LH: Did he use the grant for Michigan?

JC: Yes, Ypsilanti State Hospital. He brought Sam Gershon to this country on that grant. I wasn't quite sure whether I wasn't in conflict of interest or something or other, giving him the money. They used the money to prove to everybody's great satisfaction that simple schizophrenics are different from paranoid schizophrenics, to a great extent.

LH: Gerard is a neurophysiologist. How did he get interested in clinical psychiatry?

JC: I have no idea. I thought he was sort of getting more grandiose as he got older and having a great big program, in which he solved all the problems in schizophrenia. Then, he retired and went to California, I think.

LH: And, was lost forever.

JC: He was an entertaining and a creative guy, but I never understood what he did in zoology. He was a feisty, charming man, tough generally, to work with.

LH: Now, what would you judge to be your most significant contribution in your field?

JC: I suppose, probably, in getting the antipsychotic cooperative studies rolling. And, I'm given credit for inventing a metric for the abuse liability drugs

LH: You never trained in drug abuse, did you?

JC: Jerry Levine, who was my deputy for awhile, did.

LH: Jerry followed you at The Psychopharmacology Branch at the NIMH.

LH: Did you have much interaction with some of the other people in that period of time, say like, Nate Kline?

JC: With Nate, I had a long friendly relationship. He never got much in the way of grants out of the feds. People like Roy Grinker, who was chairman of the committee, would look at the grant, and say, "Ah, Dr. Queen". The review committee went on from there to tear it to remnants.

I finally understood that Nate was captive of a group of rather mediocre researchers. He was collecting his own civil service set, then, at Rockland State. He kept trying to put in big grants to get money for all of them and the results were these rather peculiar presentations that would turn up on my doorstep every now and then. But, I, generally, liked him.

LH: How about Heinz Lehmann? Did you know him?

JC: Oh, I knew him. Heinz and I and several other people did a site visit on Nate's Haitian Psychiatric Institute one time.

LH: So, you went to Haiti?

JC: It might have been one of the high points in my life, the week in Haiti, under old Papa Doc with whom we did business. The new clinic went up at Pompeu Bay, which was the old snake pit hospital wing.

LH: Nate was highly regarded down there, wasn't he?

JC: Yes. You also had some contact with Mike Gorman. I actually didn't dislike Mike, but I figured it was much easier to get along with people than to enter into a fight with them.

LH: Yeah, I don't think you ever had trouble with anyone.

JC: I, actually, like most people. George Crane was a little hard to like.

LH: George, if he could find you, he's going to get you.

JC: I know. I think my worst day at the Psychopharmacology Service Center was the day the Early Clinical Drug Evaluation unit people were meeting, and George presented this proposal that he wanted to analyze their data in some form or another and they all rebelled against him.

LH: You have to give him credit though that he was one of the first voices to recognize the antidepressant effect of iproniazid.

JC: Oh, yes, he, actually, probably deserved the Lasker Award for finding MAO inhibitors as antidepressants. He had observed the effect on tubercular patients on Staten Island, about the same time Nate was there.

LH: Was George working on Staten Island?

JC: No, but he was the psychiatric consultant to the TB ward where, iproniazid was first used in patients who got very happy, and he felt it was an antidepressant. He and Nate presented at the same first conference on iproniazid. Nate got a prize for it and George didn't. You could see why. I couldn't figure out which one of them deserved it. I think it should have been split, in all fairness.

LH: That's right. Is George still around?

JC: I don't know. He was retired in San Diego like five years ago. He has a son, who looks remarkably like him, whom I met a couple of times, of course.

LH: Who else were some of the people who were there early on? Did you know Hy Denber?
JC: Yes. Hy was a little aloof, a little further out, a Mr. Cool, somewhat peculiar or something or other.
LH: What about Tweenie Saints?
JC: He never, actually, had a valid medical license.
LH: He didn't? I think he was from South America, wasn't he?
JC: Cuba or somewhere or other.
LH: What about Henry Brill?
JC: I much admired Henry Brill and also George Ulett. And I have a long friendship with Max Fink.
LH: Well, Max has been around for a long while. I've got to interview him. George Ulett got into acupuncture.
JC: Yes, he got into acupuncture.
LH: He sort of dropped out of sight. How about Fritz Freyhan, do you know him?
JC: I knew Fritz reasonably well. I never was quite sure whether I liked him or not or whether he liked me or not, but we got along relatively well.
LH: He wasn't an overly friendly fellow.
JC: He was at St. Elizabeths for a while when I was in Washington.
LH: I knew he was at St. Elizabeths when Joel Elkes started, probably about 1960, wasn't it?
JC: Yes. Actually, that had something to do with my leaving Washington, as a matter of fact. I left Washington in 1967. We had been pushing about where the psychopharmacology program may go, maybe to St. Elizabeths and eventually, I was told by various higher ups that I could not extend myself that far. And, about the same time drug abuse was getting hot and Roger Meyer had come to work with me. Then, he moved over to run the beginnings of NIDA with a couple of other people and they separated drug abuse from psychopharmacology. And at that point, Milton Greenblatt invited me to come to Boston and run Boston State. My parents were getting older in Cambridge, so I figured this was a good time to leave.
LH: And, that's where you spent most of your life.
JC: Yes, in Boston. But, if they'd let me have the research ward at St. Elizabeths and hadn't taken away responsibility for drug abuse, I'd probably still be in Washington.
LH: Well, that was a nice operation for awhile. You trained quite a few people from all over the country.
JC: We had Max Hamilton in Washington for a year. Somebody finally looked at Max's personnel form, and down about the third page, there

was the question, have you ever been a member of the Communist party? And, Max marked, yes; nobody had ever noticed it before. They debated about whether to deport him instantly or ignore it and they finally decided to ignore it, which was probably the wise thing to do. The shadow of McCarthy was still loitering around. Luckily, the bureaucracy proved a lot more workable than I would have thought it might this time. I owe a vote of thanks to Sherman Ross, who took a sabbatical the year I started PSC and helped me out in research design.

LH: Wonder what ever happened to Sherman?

JC: He was at the National Academy of Sciences in charge of their psychology section, the last time I worked with him, which was like ten years ago or so. He spread himself over so many areas in psychology that he never got himself a chairmanship or a really respectable position and, then, he moved to Howard. But, he helped me get started and found me Dean Clyde to run data analysis for me and Sy Fisher, who did a lot of other things with us..

LH: Well, he gave a lot of people their start.

JC: I'm still on friendly terms with Sy. He went to the University of Texas in Galveston but spends six months in Boston.

LH: So he spends some time in Texas and some in Boston.

JC: Yeah. He had a permanent rental of a condo overlooking Boston Harbor and one of the wharfs.

LH: Well, where do you think things in the field are going?

JC: I think antipsychotic drugs are getting better and better. I think we could use a new antianxiety agent. I just got through with a study on buspirone.

LH: Do you think that buspirone type drugs are important?

JC: They ought to be and I'm not sure why they're not. I tried to talk Mead-Johnson recently into letting us restudy buspirone and see if we couldn't figure out a way of using it once a day and making it more user-friendly for primary care docs.

LH: It's never been quite as successful commercially as they'd hoped.

JC: It might be explained by the fact that it works slower than Valium (diazepam.). But, I think something ought to happen in that area .You get someone better with a benzodiazepine and when you try to withdraw the drug you get back to where you started. People on Buspar, when you withdraw it, tend to stay well and maybe even get still better.

LH: I think there's a greater interest these days than ever before in Alzheimer's. Do you see that?

JC: Well, I don't know enough about the area to tell. But, people worrying so much about it, you would think that some drug would show up.

LH: Well, maybe, that Ronald Reagan's recent revelation that he's a victim of Alzheimer's would have a certain impact on that disease as Franklin Roosevelt had on polio.

JC: It may, in fact, get the funding rolling. In a certain way, the scene in Washington is not reassuring. You can't imagine that the people in congress are going to do a lot to increase the amount of grant money, around.

LH: Well, that's rather discouraging.

JO: Yes

LH: Well, Jonathan, you've always been one of the friendliest and most jovial people in this whole field and it was a delight to talk to you and if you have anything else to say let us know.

JC: OK, I will. Thank you. I'm, glad that I might have been be able to contribute a little bit.

LH: OK.

DONALD M. GALLANT

Interviewed by Thomas A. Ban
New Orleans, Louisiana, May 7, 2001

TB: This will be an interview with Don Gallant* for the Archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the American Psychiatric Association in New Orleans. It is May 7, 2001. I'm Thomas Ban. I think we should start from the beginning: where and when were you born and if you could tell us something about your childhood, education and early interests?

DG: Well, I was born in Brooklyn, New York; I spent my first 17 years going to school in Brooklyn. My family situation was very comfortable. We were middle class. I had one sister. I went to Boys High School in Brooklyn, which was, at that time, considered to be a high school in a relatively dangerous area, Bedford-Stuyvesant, but I never had any problems. After graduating, I went to Tulane University. One of the reasons why I went to Tulane was because a doctor who lived on my block went to Tulane Medical School, and we all respected and loved him very much. So, that was my idea at that time. At Tulane, for some reason, I fell into love with physics and, so, instead of taking a pre-med course, I ended up as a physics-major. In fact, one of my idols was the Chairman of the Department of Physics, Joe Morris. He had worked on the atomic bomb and I was fascinated by him. He had lost several fingers from radiation, and I thought he really was in the forefront of research. He was my hero for awhile and I was thinking about making physics as a career. But, later on, my excitement decreased in the area of physics. The bomb had been dropped. The hydrogen bomb was being worked on and I didn't see anything really exciting or rewarding to pursue in that area. The devastating effects of the atom bomb discouraged me. So, I ended up at Tulane Medical School. In my sophomore year, Dr. Robert Heath, who was a former member of the ACNP, talked to the class. He was a charismatic man. He was very impressive, a tall good-looking man. In fact, Time Magazine had a write-up on him. They called him the Gregory Peck of psychiatry. I thought that psychiatry may be a good specialty for me. When my friends heard about that, they were very aggravated. They accused me of leaving medicine. In those days, psychoanalysis dominated American psychiatry; the Brody-Redlich concept of the schizophrenogenic mother. John Rosen wrote a book on, "Direct Analysis", dealing with psychoanalysis of schizophrenics.

* Donald M. Gallant was born in Brooklyn, New York in 1929.

I found all of this hard to accept, but this was the predominant influence in American psychiatry at that time. In fact, in order to progress academically in medical school psychiatry departments you had to be an analyst at that time. Anyway, I thought I'd spend a summer as an extern in a psychiatric hospital to see if I really enjoyed psychiatry. So, that summer, in my sophomore year, the summer of 1953, I ended up at Gowanda State Hospital, which is a state hospital about 30 miles south of Buffalo, New York. It was a fascinating experience, but also a terrifying experience. I enjoyed the patients. In fact, I had tremendous empathy for them. I really started understanding the severe incapacity of schizophrenia and psychotic depressions. At the same time, the treatment methods were unbelievable, particularly at this hospital.

TB: Tell us something about the different treatments used at the time?

DG: Insulin shock therapy was the main treatment modality that was used. One of the psychiatrists, the medical director of the hospital, came from Austria. He was using insulin shock therapy more than any other modality at that time and I, as a medical student just finishing my sophomore year, was given the temporary job of injecting 50 percent glucose in a gigantic syringe, with a "horse" needle, and trying to bring patients out of their insulin coma. It was a nerve wrecking experience, because what we used was like a "horse" syringe and I had to inject them, intravenously, before they started convulsing. Pushing the 50 percent glucose through the syringe was like pushing molasses through a syringe. And, even to this day, I get nervous when I think about it. At the same time, we saw a number of amphetamine addicts and they so closely resembled paranoid schizophrenia that I just couldn't fathom schizophrenia not being on a molecular or metabolic basis. I mean, they were just qualitatively different and seeing how the amphetamine psychosis so closely resembled the paranoid schizophrenic, I felt that psychoanalysis really was way off track. So, when I came back to Tulane, I definitely committed myself to psychiatry since it was one of the few places with an emphasis on the organic cause of schizophrenia. My empathy for the patients was very intense.

TB: Where did you do your residency?

DG: I stayed at Tulane for one special reason and that was that our department has always had a combined neurology and psychiatry department right from the very start when Dr. Heath came down here. I felt that schizophrenia was an organic metabolic problem. I wanted to get my feet on the ground, so I actually started off in neurology residency in the first year. I ended up as Chief Resident, because some of the residents were drafted into the service at that time. So I had a very good

experience in neurology and, then, went on to psychiatry. At the same time, Dr. Heath, understanding my interest in pursuing research, asked me to start interviewing some of his patients with subcortical electrodes. The number of quintuplet electrodes would vary anywhere from 80, up to as many as 120 electrodes, implanted in the hippocampus, the thalamic nuclei, pre-frontal cortex, and the limbic system, of course. I had some fascinating experiences that I can still recall today. I was always interviewing in the blind manner. We had this one-way mirror room and I would sit in the room with a patient. The electrodes were under a cap that covered the patient's head, so when he went out in public all that showed was a little cap and no one could see that he was wearing these electrodes. The wires would go through a little hole in the wall of the one- way mirror room and on the other side they did the stimulation. Even though I was blind as to time of stimulation and location, I was able to tell almost every time they stimulated the hippocampus or the amygdala. Now, this was in 1955 and 1956. Psychoanalysis still dominated academia. I remember one déjà vu experience vividly, a patient saying to me, suddenly, "you know, you look exactly like this priest that was in my church back in Baton Rouge, LA", and described the priest exactly just the way I appeared. This, to me, was unbelievably fascinating. One other person that I knew was doing this type of work was Delgado up at Yale. Every time Heath stimulated the amygdala, the patient would become uncomfortable, fearful, or angry at different times, according to the amygdala section. I thought, my god, this is real and it was a fascinating incredible experience for a young person not even out of residency. And, then, there were fascinating people that used to drop by to visit us, because they had heard of Heath's research which had been mentioned in Time Magazine. For example, we had this biochemist from Sweden by the name of Ehrensvard, an unbelievably interesting man. He had written a book on the Biochemical Adaptation of Man, along the same lines as Darwin's theory of evolution; the theory of Biochemical Evolution from the early species up to mankind. He was interested in everything. He also drank quite a bit and sometimes he would have occasional alcohol blackouts. He spent about four months with Dr. Heath. Our lab was on the second floor at the medical school. That was our research area which stayed open 20 hours a day. Heath used to be in it about 18 hours a day. It was unbelievable the amount of time he spent there. But, one evening when Heath was not there, Dr. Ehrensvard came by and he had been drinking. Now, there was only one technician on the second floor laboratory area at that time. Ehrensvard started writing formulas and the technician told us about

this the next day. He started writing formulas, first on the blackboard. Then, he kept writing the formulas onto the door, onto the next room, all around the second floor. Well, the next day we came there and we saw these formulas and we didn't know what he really intended to do, but we were scared to erase the formulas, as we thought that he may have developed some new concepts. Meanwhile, he was drying out somewhere. So we kept the formulas on the wall for about a day and a half or two days, trying to figure out what his intentions were. Finally, he shows up about two days later and he looks and he doesn't remember writing them. It was an alcohol blackout. And, not remembering having done this, he said he just didn't understand what he wrote, so we were finally able to erase it and clean up. The Dean was very disturbed about all of this going on in the research area as he suspected what had happened. I don't know how much I should tell you about Ehrenswand.

TB: As much as you wish.

DG: I mean he was really unusual. He was a wonderful man. One day, he was down at the French Market, Café Du Monde, having coffee and doughnuts with two of our lab technicians. And, in those days, Café Du Monde used to have these gigantic sugar bowls that they'd chain to the table to keep people from stealing these sugar bowls. Well, Ehrensvard was insulted. He thought that there should be trust and that this was unacceptable to him. So he picked up the sugar bowl, ripped it off the table and ran away. They chased him and caught him. They called the police and they wanted to lock him up, but Dr. Heath intervened and stopped it from happening. He was attracted to Heath's work on Taraxein.

TB: Am I correct that we are towards the end of the 1950s? Could we go a little bit back in time?

DG: Right, right.

TB: It seems to be that Bob Heath had a major impact on your career.

DG: Oh, yes.

TB: Probably, he was the single most important person for you deciding to become a psychiatrist?

DG: I would say, yes.

TB: You attended his lectures as a medical student and started psychiatry before the introduction of the new psychotropic drugs?

DG: Yes.

TB: You talked about insulin coma therapy and also about seeing amphetamine addicts who resembled paranoid schizophrenics. Is there anything else you would like to tell us about that period?

DG: Well, actually, I remember one incident when I was extremely embarrassed at Gowanda State Hospital. I haven't thought about this in some time, but there are some incidents that always stay with you. One of our assignments was to work up some of the patients and present them to the staff and one of the patients I worked up was a man about 77 or 78 years of age. He had some problems with memory, some problems of orientation and he, in addition to having these memory problems, which were primarily organic, he also told me, about some delusional material about some oil wells he owned in New York State. Having grown up in Brooklyn, New York, I had never heard of any oil wells in New York State. When I presented him to staff, I presented him as a dementia case and, also, mentioned his delusions about the oil wells, and it became part of his diagnosis. Well, about a week later, his son shows up at the hospital and, yes, he had oil wells in New York State. I never got over that. So, I think it was a good lesson. It always made me hold back and not be too impulsive in my evaluations of patients or of people. That memory, of course, has stayed with me all of these years.

TB: Was this in the early 1950s, about '53?

DG: Right.

TB: Didn't you enter the army after medical school?

DG: No, after residency, I was drafted into the Air Force and, since I had training in neurology and psychiatry, they decided that I could do both. So they sent me over to Clark Air Force Base in the Philippines, which was a base, at that time, of about 25,000 people, including civilians and families associated with the base. In addition, I had to be responsible for treating a lot of US Government employees living in Southeast Asia. I was the only psychiatrist in that area at that time, from 1959 to '61. That was before Vietnam blew up. I was the only psychiatrist for the United States Air Force, Navy, Marines, CIA, ICA, in Southeast Asia, in addition to Clark Air Force Base and Subic Bay. That's a lot of people that I was responsible for. In fact, I had documented and kept my charts because of the tremendous experience that I was offered. I saw close to 1100 patients in two years. At the same time, I had read some of Paul Wender's work with dextroamphetamine in hyperactive attention deficit disorder. This was published about 1958. We had children in a school on our Air Force base, and we had a number of kids, whom I diagnosed as hyperactive attention deficit disorder. I used dextroamphetamine, 5 or 10 milligrams twice a day, and, in a number of cases, I had rewarding results for the child, school teacher, and parents. I think that was one of the events that steered me towards psychopharmacology because it was almost like magic. In fact, one

of my associations, talking about magic, was my first year residency at Charity Hospital in 1955. In those days, in Charity Hospital, we had 1800 patients. Alcoholic withdrawal encephalopathy was not unusual because in those days the patients were left lying out in the street for several days and nobody would bring them in. By the time they came in, they were really deteriorated and in a number of cases, just giving them thiamine, 50 or 100 milligrams intravenously, would eliminate the ataxia and ophthalmoplegia of a Wernicke's Encephalopathy within 30 to 60 minutes, giving me a wonderful sensation of being a doctor, as well as a psychiatrist, and, also, making me feel that the medications had a real definite use. Of course, some of these patients would have residual memory symptoms. It was just amazing how fast the ophthalmoplegia and the ataxia would clear up. It was a tremendous experience. I should mention that we had some excellent faculty. We had Russ Monroe, who went on to become Chairman of the Department of Psychiatry up at the University of Maryland, an excellent clinical person. We had Harold Lief, who went up to Philadelphia to head up the Family Research Unit there at the University of Pennsylvania and other really outstanding faculty in Neurology. Heath, himself, was boarded both in Neurology and in Psychiatry, as well as having his training in Psychoanalysis at Columbia. Some of our medical students such as Steve Paul and Peter Rabins published their first articles under my supervision and residents such as Chuck O'Brien went on to become outstanding clinical researchers.

TB: Wasn't Heath trained by Sandor Rado?

DG: Yes, yes, he was trained by Rado. In fact, Rado was one of Heath's heroes. At one time, Heath had the fantasy of trying to tie the biochemical concepts of psychiatry with the adaptational theory of psychoanalysis and Rado, of course, was very, very much interested in it. Rado came down a number of times to lecture to us and he was a very impressive man even though he wasn't that biochemically oriented. He was very impressive in the way he did patient interviews. He had a wonderful touch and just watching him was a learning experience.

TB: So, you knew Sandor Rado?

DG: Yes, a wonderful man.

TB: Can you tell us a little bit more about Bob Heath? No one talks about him any longer.

DG: I know. I get sort of disenchanted or disappointed when I look at some of the current articles in the literature that really evolved out of some of the work that he did. His papers are not even referenced in some of these articles. The neurophysiologic and biochemical concepts of dopamine transports and the cerebellum; his organic approach to schizophrenia

and just the basic stuff we were able to report as far as the various physiologic functions of the hippocampus, amygdala and the striatum had not been reported prior to 1947-1948.

TB: Didn't he start his research in New York at Columbia?

DG: He had done work on the Columbia Greystone project, trying to find some other way of treating schizophrenia, neurosurgically, instead of doing frontal lobotomies, which were unbelievably damaging. They were trying to do partial temporal lobectomies. He also was well known around Columbia because of his interest both in neurology and psychiatry. He was only about 35 at the time when our Dean at Tulane Medical School was looking to start up the department of psychiatry. We didn't have one until Heath came down, and this was before I started medical school. It was about 1947 or so that Dean Lapham asked some people at Columbia if they would recommend anyone who might make a good chairman and they mentioned Bob's name. In the next day or so, the Dean went to Atlantic City. He was lying on the beach next to somebody and started talking about New Orleans and Tulane and mentioned that he was looking for a chairman. The person he was lying next to was Bob Heath. And, that's how Heath became down as chairman of psychiatry and neurology. He said neurology would be under psychiatry, not medicine, the way it was in other medical schools. So, that was the beginning of our department at that time. I think he was department chairman longer than almost anybody else in the history of medical schools in this country.

TB: When did he die?

DG: He died last year. He had congestive heart failure. In fact, some of the residents went to interview him about a week or two before he died; put him on tape about his experiences, his memories about the past and how he became involved in psychiatry and research. I think he also mentioned one or two funny stories about his subcortical electrode patients. The patients he selected were either drug refractory epileptics that did not respond well to anticonvulsive medication or severely ill chronic schizophrenic patients that were not responding at all to treatment. He would do these subcortical electrode implantations with the idea that eventually he would do a temporal lobectomy if they didn't respond to stimulating treatment. Anyway, one of the patients, a temporal lobe epileptic patient, ran away, left town and went to the University of Chicago. Danny Freedman was Chairman of the Department of Psychiatry at that time. The patient tried to sell himself and his hardware for $5,000 to Danny. Freedman, of course, had no idea what was going on. All he saw was somebody with a cap on his head so he called Dr. Heath and

said that he had this patient who was trying to sell himself. He said, "Not only do I not want to buy him; I don't have the money, either." So he arranged for the patient to be accompanied back to New Orleans. Things were always happening around Heath, he was a very impulsive man at times.

TB: Let me ask you about your early research. Didn't you work in the 1950s with hypoglycemic agents?

DG: Yes, right. The idea was to see if you could lower the blood sugar, gradually, and, at the same time get a therapeutic effect, but that turned out to be totally nil. It was no better than placebo.

TB: Didn't you get involved also in group therapy in those years?

DG: I became involved in group therapy with alcoholics and drug addicts who are much more amenable to the approach. With schizophrenics, I could never really do group therapy. That would be a ward meeting, it wasn't group therapy.

TB: You also did some research in the 1950s with dextroamphetamine, didn't you?

DG: Right. Paul Wender, of course, was the first person who published on its use in ADHD. That was in the American Journal of Psychiatry in about 1956 or 1957, right before I went to the Philippines.

TB: Wasn't that your first paper?

DG: That was my first publication and it was in an Air Force Medical Journal.

TB: What did you find with dextroamphetamine?

DG: We had excellent results. The attention span increased; hyperactivity decreased. I only took classical cases of ADHD and had about 4 or 5 of them. It wasn't a large study, but it was a very impressive response that made me realize that psychopharmacology, even on that relatively primitive basis, would be very promising as far as helping patients.

TB: Are you board certified in both, psychiatry and neurology?

DG: I was board-eligible in both specialties, but I only certified in psychiatry. After taking my psychiatry certification, I just didn't want to go through the testing again, memorizing and so forth, but I felt that having neurology first helped get my feet on the ground. When medical students ask me about going into psychiatry, I usually recommend a year in neurology, to deal with the structure, before they get into something more subjective. My experiences in the Air Force, having such a large number of patients, was really good for me. By the time I left the Air Force, I had more clinical experiences in two years than I would have had in a clinical practice in the states in four or five years. I was involved in different things; we had a fellow by the name of McCann, a prisoner of the Communist Chinese. He was supposedly a second hand car

salesman in Shanghai, China, and when the Communist Chinese took over in 1949, they couldn't figure out what a Caucasian car salesman was doing in Shanghai. They locked him up when they realized he was a CIA agent and he was still in prison by 1959. His wife heard he had lung cancer, so she appealed to Mao on a hardship basis to see if he would release McCann; and he said yes, if we would come and get him. Well, I was the only psychiatrist in that area, so they sent me and the Colonel of our hospital, Colonel Gehring, to Hong Kong. I had some peculiar experiences there, to give you an idea of the CIA. This was in 1959 and the CIA in Hong Kong wanted to keep what we were doing secret, so they arranged for me to meet them in a bar in some very poor Chinese area. There were no Caucasians in that section of Hong Kong, and I didn't have anything to wear but an Air Force uniform. So I would be wearing my Air Force uniform in supposed secrecy and they'd say McCann is coming tomorrow. The next day the Hong Kong newspapers would say McCann is not due till Thursday. Sure enough, the newspapers were right. The CIA was wrong. This went on for about 3 days. Finally, he showed up at the border on Thursday. I was sent to see if he was brainwashed. Well, the poor man wasn't brainwashed but he did have lung cancer which had metastasized to the brain. But, his wife felt comfortable since he died on what was considered to be US soil rather than in a Communist prison cell. I had a number of experiences like that, being the only psychiatrist in that area, as well as the only neurologist. It was very, very interesting.

TB: What did you do when you came back from the Philippines?

DG: I started off with a psychopharmacology research grant. Bob Felix, who was head of NIH, selected Jonathan Cole to head up the psychopharmacology research branch and they had funding for about 19 or 20 ECDEU centers. Jonathan Cole was looking for people to apply and he called up Bob Heath, realizing Bob was interested in the organic aspects of psychiatry. Bob applied with Mel Bishop. Mel Bishop was a psychologist I thought was tremendously talented, really an excellent person. And, Heath wrote up the grant. By the time I came back, the grant had been accepted, so Bob called Jon Cole to see if he would put my name as the principal investigator. Jon Cole really took a chance on me, because I'd only had a couple of publications from the Air Force. I owe a great deal to Jonathan Cole because of his taking a chance on me. He allowed me to be the principal investigator and Mel Bishop the co-principal. If it weren't for Mel I wouldn't have known anything about statistics. I still know nothing, but I know a little bit of nothing, rather than absolutely nothing. Mel was of tremendous help; we worked very

well together for many years. In fact, Mel is responsible for one of my most positive memories concerning a compliment made to me at an ACNP meeting. Correct me if I'm wrong, but it was in January of 1964, I think it was January at that time, when they had the first meetings. Joe Zubin was a superior psychologist at NYU, very well respected. At that time we didn't have the psychiatric rating scales standardized yet and were only starting to use the BPRS. Instead we used the Tulane Test Battery, which had a lot of statistical evaluations. So I presented the data from the Tulane Test Battery we used for evaluating schizophrenic patients and their response to medication relying on Mel Bishop's having educated me. At the end of my presentation, Joe Zubin complimented and said, "It's nice to see Tulane has a good psychologist." I explained, "I'm not a psychologist, I'm a psychiatrist." He was surprised! I felt that was the greatest compliment in the world; someone like Joe Zubin thought I was a psychologist! I still remember that.

TB: Can you tell us about the Tulane Test Battery?

DG: Well, it was very primitive and simple. Mel extracted data from one of our organic mental status exams and quantified it. He also added about 8 or 10 questions dealing with psychoses that we threw. He took the WAIS scale, the eye-hand coordination and the IQ parts of the test and incorporated them as part of the scoring of the Test Battery.

TB: In what kind of patient populations did you use the Battery?

DG: We had several different patient populations. We had an outpatient population at Charity Hospital in New Orleans, where we ran a psychiatry service with LSU Medical School, but Tulane was more involved with patients in the State program even though we were a private medical school. So, I was running this schizophrenic research unit at East Louisiana State Hospital up in Jackson, Louisiana, a building given to us by the state. Bob Heath was a very good politician when it came to Louisiana politics and we had 120 patients, 60 male and 60 female patients evaluated for transfer to our research unit. These patients were unbelievably severely chronic. Their mean duration of hospitalization was about 22 years, with a standard deviation of only about 4 years. They had not been treated by anyone, just warehoused before they came onto our unit. East Louisiana State Hospital was out in the woods, totally isolated, about 115 miles from New Orleans, with no good roads going up there. I used to go there twice a week and it took me about two and a half hours each way, five hours of travel. So, this population, when we did quantitative organic testing, resembled dementia patients more than acute schizophrenic patients on some tests. We had some data along those lines but never published it. The families had given

up on these patients; they would never visit, even though we tried to get telephone consents from the families to include the patients in our studies. In addition, every study had to have judicial consent. So, the test battery had to be a primitive one for that type of population. In fact, when the BPRS was standardized by Overall and Gorham, we could not use it in the way it was standardized for acute schizophrenic populations. We had to modify it, because on a lot of items we could not base the score on a verbal response from our patients. So we changed them to observation items. So we modified the BPRS for our chronic population, while we used the original BPRS for our acute schizophrenic population at the hospital in Mandeville, Louisiana. I also had my alcoholic and drug abuse population at Mandeville. We had these four different populations for psychopharmacology studies and so I was involved in quite a few studies with Mel Bishop. Without him, I could never have functioned. We were so busy, so preoccupied, so involved that when I looked up one day we had published about 25 papers in just two years! I guess that's what helped me to be admitted to the ACNP in 1963. I don't think I would normally have been admitted but in 1963 there were fewer people applying and I had those 25 publications which was good as far as psychopharmacology was concerned.

TB: Was the research supported by the ECDEU grant your primary activity in those years?

DG: No, I had several primary activities. Looking back, I think they should have locked me up. I was unbelievably hyperactive and with someone like Mel, who was also productive, both of us were overdoing things. I would start off my days at about 3:30 in the morning then I would go to Jackson, do my research evaluations. I liked to get there before my daytime and research staff. I never had to criticize them. They just made it their business to come in on time, because I was waiting for them. It was the best method I ever found for dealing with staff. If they came late or started goofing off, it was very apparent to me and to them. Then, after I done my evaluations in the morning, I would drive to my alcohol and drug abuse center at Mandeville for the afternoon to do evaluations there; I was the only psychiatrist treating alcohol and drug abusers in southern Louisiana for the state. At Mandeville, I had a 32 bed unit I ran by myself with a good nursing staff. After my work at that unit, I drove back to Tulane Medical School to catch up on correspondence. Later on, I also became medical director of student education at Tulane as a third job. So, I would get home by about 6:30-7:00 in the evening, write my research papers, spend insufficient time with my family; go to bed by 11:00 o'clock and, then be up again at 3:30

am. This went on for years, and that is why I say they should have locked me up. But, I was enjoying it. I realize I was very fortunate to go into psychiatry and lucky to stumble into it the way I did. To have the opportunity to do patient care at the same time on the alcohol and drug abuse unit was fascinating. I ran the alcohol and drug abuse clinic here in New Orleans and did quite a few clinical studies in that population as well as in schizophrenic patients. I did also clinical studies in outpatients with anxiety and depression in the population at the Charity Hospital.

TB: Those were obviously very productive years. Could you tell us more about your research related to ECDEU?

DG: Jon Cole was the heart and soul of ECDEU; if he had not been given that job, it could have fallen flat. He was so enthusiastic and so pleasant and easy to deal with. We had a bunch of characters, each one of us representing different early clinical drug evaluation units, and we presented our findings, argued, and agreed or disagreed. I'll never forget that one time in 1962 we received a drug from Janssen, called trifluperidol. I should say that our chronic schizophrenic population had almost no placebo response. We did about four or five double blind studies in 1961 and 1962 and we never had more than a ten percent placebo response.

TB: Didn't you publish on that work?

DG: Yes, we did. You have a better memory than I do. I think it was in the Archives. Anyway, I only had 12 patients on trifluperidol the first time. I presented our data at the ECDU meeting and one or two of the other investigators, who were somewhat older than me, criticized me for sticking my neck out because I was saying this was a new active therapeutic drug and not just one of those "me, too" drugs. Apparently, somebody at NYU had an acute schizophrenic population and couldn't really see a difference between the drug and placebo. So, they also disagreed. I felt pretty shaken about it. We went ahead and did the double blind study and, sure enough, trifluperidol was really a good antipsychotic. I believe that later on it showed some pancreatic problems in mice and it never became commercially available in this country. That was the first butyrophenone we studied and Paul Janssen wrote me a very nice letter, thanking me for sticking to my guns. Obviously, it helped his company. That was just one of the experiences I had with ECDEU. The group functioned very well, I thought. It was a group that traded experiences, information and data so all of us grew from the experience. Again, without Jon Cole, I don't think it would have evolved so well.

TB: Would you like to mention a few people who were involved with the ECDEU program in those years?

DG: George Simpson, you and Heinz Lehmann. Herman Denbar, I remember very well. Sidney Merlis and also Sidney Malitz from Columbia were there. I can't remember anybody from the West Coast. So it was all people from the northeast and our unit in the south.

TB: Was your unit one of the first in the ECDEU network?

DG: Yes, I think it was. Originally, the grant was directed totally towards schizophrenia, but we opened it up with my alcohol and drug abuse population in Mandeville and depression/anxiety studies at Charity Hospital in New Orleans. We dried out our alcoholic inpatient population for four weeks or so and, then, did anxiety studies in those who had residual anxiety. These were double blind studies. In one study in 1969 we compared doxepin vs. diazepam vs. placebo, and doxepin came out looking as good as diazepam for its anxiolytic effect; we published that in the Journal of Psychopharmacology. At first, other investigators didn't pay any attention to these findings. I didn't want to use benzodiazepines in the alcoholic population, who did have a tendency to misuse those drugs. From that point on I was using tricyclics, and later on SSRI's, for decreasing anxiety in generalized anxiety disorders, rather than the benzodiazepines. Later on, I think in 1990, Lancet published an article on the anxiolytic properties of doxepin. So, for many years I was disappointed other people had not started using the tricyclics for anxiety.

TB: We also studied the effect of doxepin in anxiety disorders in the 1970s.

DG: Oh, you did?

TB: We developed with Heinz Lehmann a conflict tolerance test and doxepin increased conflict tolerance just as benzodiazepines did. Can you mention other drugs you studied in those years?

DG: Haloperidol, of course. A lot of people were involved with haloperidol at the same time we were. In fact, there was a separate haloperidol meeting that went on in Miami. I remember we were all reporting about the same results; that it was an excellent new drug and the side-effects were minimal to moderate while sedation was practically lacking. So it was a much more comfortable drug than chlorpromazine. Molindone was another drug that was interesting to study and, then, butaperazine, but nothing much came of that. That was an antipsychotic.

TB: Didn't you work with mesoridazine?

DG: That was a bad situation. I don't know if you're aware of the story, but about 1970 or 1972, we worked with mesoridazine. Two problems with that; one was granulocytopenia reported in the literature and we

were able to confirm that. The other one was the prolongation of the QTc interval, so we reported on the prolongation of QTc interval with mesoridazine which we could detect double blinded. We also double blinded thioridazine after that against thiothixine and placebo using a control group of my attendants on the research unit. Lo and behold, only one of the 13 thiothixine patients had prolongation of the QTc, and one out of 13 control attendants also had prolongation after 8 weeks. But 13 out of 13 patients on 800 milligrams a day of thioridazine, and 7 of 13 on 400 milligrams a day had prolongation of the Q-T interval. We published that. In fact, my cardiology fellow that read the EKG's could identify thioridazine, blind. He did this with George Simpson's patients, also. George was fascinated. After we published, somebody from Sandoz called and started yelling on the phone at me, criticizing me, saying I was unethical for publishing the data. This was 1972, and I was shocked that someone from a pharmaceutical firm would start telling me I'm unethical for publishing these findings, which were unbelievably solid. They were controlled double blind studies. The EKG's were read blind and the cardiologist reading the EKG's did not know to what drug group the patient belonged. It was solid, solid data and Sandoz Company never made any mention about it. It was published in the American Journal of Psychiatry I think but nobody paid much attention to it in the literature. In the last few years people have been talking about it again, but the data has been out there for 20 or 30 years.

TB: Cardiac conductance changes with thioridazine, structurally closely related to mesoridazine, were first reported in the early 1960s.

DG: Early 1960's?

TB: Three patients died in Kingston, Canada while treated with thioridazine and it was attributed to cardiac conductance changes caused by the drug.

DG: Sudden death.

TB: Sandoz became interested at the time in the effects of thioridazine on the EKG and in a crossover study with trifluperazine and chlorpromazine we showed, and published in 1963, that it produces prolongation of the QT interval. Lou Gottschalk had similar findings a little bit later and he tried to identify the metabolites responsible for the cardiac changes. For many years these findings were dismissed. Now, there is a warning.

DG: That's the only time I ever had somebody call me up and start telling me I was unethical and the first time I had somebody from a pharmaceutical firm try to prevent publication. It's instilled in my memory.

TB: Didn't you subsequently study the effects of several psychotropic drugs on the EKG?

DG: We did it routinely at the very beginning and also with the tricyclics. We saw a few changes. The type of studies that we did would vary from East Louisiana State Hospital in Jackson to Southeast Louisiana State Hospital in Mandeville to Charity Hospital in New Orleans. They were very different types of studies. When it came to selecting patients for the ELSH research unit in Jackson, LA, there was a problem. Patients in the state hospitals were segregated, so we had a choice. Either we were going to transfer Caucasian patients to our research unit or transfer black patients to the research unit. Even though Louisiana was segregated, the federal government wasn't. So with a federal grant, we decided that we better just do our research on white patients. Thus, our schizophrenic research unit was all Caucasian. It was a paradox, in a sense. Here you have a segregated society and we're doing research on the Caucasians, who aren't in favor of integration. We were able to have both groups of patients, blacks and whites, at Charity Hospital but in separate clinics. We saw differences in placebo response which we were very afraid to publish for fear people might think we were prejudiced against blacks. We had no control over that state-imposed system. We had to do it that way or else be arrested. At one time, we did a double blind studies of a compound called JB8181, (desipramine), vs. placebo in the white clinic and in the black clinic, about 20 to 30 patients in each group. Now, the black and white populations in Charity Hospital, this is 1963 or so, differed significantly, personality-wise. In those days, Charity Hospital was called Mother Charity, and it served the entire population that was poor. The black patients had a positive identification at that time for Charity. The whites at Charity Hospital were there because they couldn't afford private treatment and they were much more negative. These two populations had a significant difference in placebo response. With desipramine vs. placebo in our white population, we saw a significant drug-placebo difference, but in our black population, because of the significant placebo response, it was about 55 percent, we could see no significant difference between drug and placebo. So, when we added up the data, we saw only a slight difference of drug over placebo. Were it not for segregation, we would have never been positive about the antidepressant properties of desipramine. So we had peculiar clinical drug experiences during that period. It was a very unusual time for New Orleans and the State and we were caught in the middle concerning the way we were doing research.

TB: So, you had been involved in studying antidepressants as well from the very beginning?

DG: Oh yes. We had some compounds that were serotonin antagonists that we tried out in our population, but didn't get any real good positive results using them. At one time we collaborated with Leo Hollister on a protein fractionation serum project. Heath was interested in that area and Leo was interested a little bit in that area, so we collaborated on our patient populations, but, again, we saw no significant difference between our controls and our schizophrenics. We reported those findings because I felt it was important to report on negative results, as well as positive. Except for the Sandoz incident, we never had unusual pressure from pharmaceutical firms. With the present terrible conflict of interest by pharmaceutical firms and investigators, I do believe that bringing back the government financed ECDEU units would help to clear the air. When I reflect back on these different populations, I feel that most interesting was the significant differences between our acute and chronic schizophrenics patients. We called them Type 1 and Type 2 schizophrenics, according to Crow, and, also, our alcohol and drug abuse populations where we reported on some of the dual diagnosis problems. Depression in our alcoholics, of course, was much higher than it was in our non-alcoholic population. So, they were very good populations for doing antidepressant studies.

TB: In the early years you collaborated with Heath, didn't you? When did you stop working with him?

DG: I reached a point with Heath when I was not able to really collaborate with him after about 1964 or 1965. We had a difficult incident that was a sort of inappropriate situation. He accused me of stealing his research, in which I had no interest. After that, it was sad, but I told him I could stay at Tulane only if we did separate work. This incident occurred over a patient with diabetes insipidus, of all things. We had a patient in the VA Hospital and one patient at Charity. Both had lesions in the mid brain area. One patient had a temporal lobe tumor associated with diabetes insipidus and the other patient had multiple small infarcts. I was accumulating the data for joint publication with Heath as the lead author when I was still a young faculty person. He had been my teacher in medical school, my mentor in residency, and I took it for granted he would be the lead author on this paper, which wasn't covering a lot of territory on diabetes insipidus. It was not that important to psychiatry, but he blew up at me, thinking I was going to take credit for the paper. It was a very bad scene. He was overly suspicious. Russ Monroe left and Harold Lief left, after some years of difficulty with Bob Heath. I should say that at other times it was fine and easy to get along with him. At other times, it wasn't that easy.

TB: But you did publish several papers with him before you parted?

DG: He believed that the area between the limbic and the prefrontal cortex, was the key to schizophrenia, and he was focused on that. He would see occasional spiking in the schizophrenic patients with subcortical electrodes from that area, which he didn't obtain from the temporal lobe levels. That was interesting and he published the data. We did the antibody study, the protein fractionation study. But outside of those studies, there was very little. I felt bad about it, but it's amazing the way we both functioned separately after 1965 and were friendly outside of the investigational work. We got along quite well. It was almost as if he forgot about the incident and to him it was over. I never forgot the incident, obviously, and to me, it was never completely over. It was very hurtful for a long period of time, but I always defended him in public. People either admired and respected him for what he was doing, or else, they thought he was untrustworthy and didn't trust his data. He did have one large research problem, which was "controls". He would not pay enough attention to having good controls for his studies. Talking about controls, there was an incident concerning Heinz Lehmann. Heinz Lehmann, who I considered to be a very gracious, friendly, open person came down as part of a site visit to look at Heath's work. On our research unit Heath grabbed him and before Lehmann knew what was happening, Heath had blood being drawn, using Lehmann as a control. And, he didn't even object. Later on, when it came to evaluating Heath's Taraxein work, almost everybody was totally negative about it. But Lehmann held back for awhile and said, give him a chance. You know Lehmann much better than I ever knew him, but I think that's the way he was. That was a terrible joke, but Heath would do things like this. He was very impulsive.

TB: Could you tell us more about your research related to ECDEU? You were involved with ECDEU for well over a decade.

DG: 16 or 17 years, something like that.

TB: It was a very, very productive period in your life.

DG: There was an interesting thing about being productive and receiving ECDEU support. ECDEU gave us grant support, not for just doing the drug studies, but also to support my base salary at Tulane. So it enabled me to do a lot of work outside of ECDEU. It was of fantastic help in all areas of my clinical experiences, not just in drug studies. The ECDEU formula produced quite a few outstanding people, Arnold Friedhoff, Sam Gershon, Sid Malitz, Max Fink, who were very good. So, it was very rewarding and stimulating, very good people, for the most part. The ECDEU also permitted us to do our anti-anxiety and

our antidepressant studies. We even did a study with metronidazole in alcoholics that was a "spin off" from our ECDEU grant

TB: Tell us something about your findings with metronidazole in alcoholics?

DG: This was interesting. We did a double blind study vs. placebo and found no difference. It was a 6 month study and at the end we found no difference in the abstinence rate or the number of drinking days. Even though, theoretically, metronidazole might inhibit ethanol to some extent, it didn't perform clinically in the area of alcoholism. Until that time, there weren't too many controlled research studies on the psychopharmacologic aspects of alcoholism. In fact, these protocols led to some comparison clinical studies with "criminal alcoholics", with good results. I was disappointed that our data was not utililized by other substance abuse investigators. Our data is even important for the present time. What we meant by "criminal alcoholics" were patients coming out of our state penitentiary in Angola, which is a pretty bad state penitentiary; back in 1969 it was horrible. These patients had committed major crimes, such as homicide, rape, armed robbery, directly or indirectly associated with alcohol problems. They were randomly distributed into two groups. This was a small study, only about 24 patients. One group had to come regularly every week to the clinic for treatment and take Antabuse (disulfiram). If they got involved in the project, they were given early release. Otherwise, they had to serve their regular time, so it was free choice. If they chose early release, then they were randomly distributed, one group to come to us for at least 6 months in addition to taking Antabuse. We needed the 6 months to work out their initial anger about the enforcement of treatment. The other group had to come to our clinic only once, in addition to the regular parole, and we had to talk them into coming on a voluntary basis. At the end of one year, even though it was a small study the results were significantly different. In the voluntary group, only one out of 12 patients was doing okay. Of these 12 patients, 9 were back in jail at the time of the one year follow-up and 2 were at large out of state for breaking parole. In the compulsory treatment group, about 7 or 8 out of the 11 or 12 were doing well. It was small but it really told us something. If you have enough of a hammer to hang over the "criminal alcoholic" or probably the "criminal drug addict" and the compulsory treatment is long enough to work out the anger about being forced to get treatment, it's very worthwhile. This data was published in 1969, but nobody took advantage of that data that I know of until recently. New York State is now involved in that type of project, but it was disappointing that people did not take it up in the 1960's. We did similar projects along these

lines. Remember Sam Guze? He was chairman of the Department of Psychiatry at Washington University Medical School in St. Louis. He was an excellent person who did some research on crime and poverty and was responsible for getting the "revolving door alcoholic" grant. I was running a free clinic at the Fischer Project, which was a low-income housing project in New Orleans, at that time. I worked there Friday afternoons and all day Saturdays.

TB: You became very much involved in the Fischer project, didn't you?

DG: Right. This Fischer Project had no methadone clinic, no medical clinic, nothing, so I started a general medical clinic. Sam Guze published an article; I think it was in the Archives, on people from the poverty area in St. Louis, a black project area, who ended up in jail. What he reported was, if a child missed 10 days in a row at school in the first grade and missed 10 days in a row of the second grade, he or she was twice as likely to end up in jail as somebody who had not had that type of absentee attendance. So, we took those two pieces of data and, having spare time on my hands, we hired an African-American woman, who had a car, and paid her about $30.00 a week. We had contact with the school principal in the Treme area in New Orleans who gave us the attendance records. If a kid missed 10 days of school in a row in the first grade and 10 days of school in a row in the second grade, we had this woman pick up the kids and bring them to school. It was amazing the way their grades were jumping up in six weeks, fascinating just from coming to school regularly. To show you how important that small piece of data is, there were two little girls who missed about 20 days of school in a row in the first grade and about 20 days of school in a row in the second grade, and by the time our lady went to pick them up we learned that their father had committed suicide the previous week. The wife had died from cancer the year before and he was deeply depressed, not paying attention to the children. They were running wild. Missing school in those two pieces of time usually meant that there was a tremendously fragmented home situation that had to be adjusted immediately. That was spin-off from the time that was allowed to me by having my base salary supported by the grant. We were doing our obligated research work, but also doing "spin off" work at the same time. At the Fischer Project, we were paying for our patients' methadone; the heroin addicts had to come over from the west bank on the other side of the Mississippi River, to get their methadone every day.

TB: Could you elaborate further on this?

DG: The clinic was a general medical clinic. We made contact with the population to get them to realize that we were not out just to do research

with them. We also used that population to teach my medical students about delivering medical care in poverty areas. If the patients came to the methadone clinic on a regular basis and stayed clean for two months, we would get them a job. If they stayed on the job for three months, which meant that they were clean for five months, we would pay for their expenses to move out of the project. When they reached that point, most of them would not want to leave the project. That was one of the saddest discoveries I ever had. They were too scared to move. It was their comfortable cocoon. They'd been there too long and, thus, they wanted to stay for the rest of their lives. That's where all the IV shooting up was going on and all the selling in the Fischer Project. So I felt a bit disenchanted by my experience after four years or so, and realized we came to these people too late in the course of their illness. They just couldn't make it socially outside that environment. That was a very depressing experience, to say the least. I undertook all of these clinical experiences for my own learning. For teaching, this was very, very important and still is important to me now.

TB: Weren't you the Director of Education in the department?

DG: Yes.

TB: From the early 1960's?

DG: No, later on. I became Director of Medical School teaching in psychiatry in the late 1970's or early 1980's. The previous director had left and they had nobody to take over. I enjoyed medical school teaching and I had some positive reward out of it. I call it "selfish-selflessness". They had what they call The Owl Club at Tulane; if you're an outstanding teacher, you'd get an award every year. I had been getting this award every year for 15 years or so, and, in fact, the graduating class gave me an outstanding award for medical student teaching. That positive feedback is essential if you're going to really keep functioning and enjoying what you're doing. Being the Director of Medical School Education in Psychiatry was a real challenge. To get full time faculty to put the hours of teaching in became more and more difficult, because those people who did not have grants to support their base salaries would have to either see private patients or do consultation work with outside institutions. It became very difficult getting people to volunteer to do teaching. Sometimes, I felt like a total bully, trying to get them to spend an extra hour or two a week. It was rewarding, but also frustrating. Nowadays, it's still a problem, and the present Director of medical school education in psychiatry still has problems getting people to give lectures since it takes them away from their income, much more than back in the in the 1960's and 1970's, when we had federal grants to back us up and the

grants were easy to get. So, when old people like me come down here to do some teaching they're very grateful, because I'm helping them have extra hours to support their income.

TB: So you had grants for teaching. But you also had support for some of your other projects.

DG: We had the grant to do the compulsory treatment study with alcoholics. In fact, we did another one after the criminal alcoholic study. We did a "revolving door" alcoholic municipal study. That was federal grant support.

TB: When was that?

DG: It was about 1972. The criminal alcoholic study was in 1969. We thought compulsory treatment might also work for the "revolving door" alcoholics. Now, there is a difference between these populations. The revolving door alcoholic or skid row alcoholic is less dangerous to the community than the criminal alcoholic, but we found out he's less treatable. This was a large 100 patient study funded by a separate grant. We had 50 patients come to our inpatient program for four or five weeks treatment, then got them a job and paid for a place to stay. That was our compulsory treatment group. If they missed a clinic visit, they went back and served the remainder of their sentence, which was usually between 60 and 90 days in Parish Prison, a totally different type of club to hold over someone's head, compared to Angola State Penitentiary for the "criminal alcoholics". The voluntary group just had to come to us once a week in the clinic and if they decided not to come, they were dropped. We did extensive follow up. Now, doing follow up on "skid row" alcoholics is not easy, because they move around a lot; although, in New Orleans, they liked the climate, so many of them stayed here. But they still moved around. So, we hired someone who had some detective skills to locate our patients for follow up; looking for them in Arizona prisons, everywhere, using telephone books, school systems or what not. He was able to locate, it sounds impossible, more than 80 percent of our patients in a one year follow up, but it turns out the compulsory treatment for this group was a total waste of time, compared to the "criminal alcoholic" group. There were real differences. This group had nothing to lose. They had already been arrested an average of 50 times or more. We had one person, named "Whitey," who been arrested close to a thousand times. I know that sounds impossible, but it's true. When he needed a place to stay, he would call the police and tell them there's a drunk lying in the street and they should pick him up because he's blocking the store entrance. Then he would lie down in the street. They'd come, pick him up and take him to Parish Prison, where the

food was pretty good in those years. We had a psychiatric evaluation profile, the PEP. Jerry Levine standardized this, by the way. It has a factor in it that is "overly optimistic". These "skid row" patients scored significantly higher on the "overly optimistic" scale compared to our "criminal alcoholics". They thought, "I'm going to make it"; "I can do it"; "No problem"; "I'm off alcohol the rest of my life"; this type of unrealistic approach was one factor. Another factor was "self-esteem". They scored very low on "self-esteem". So this combination of very "low self esteem", but "overly optimistic" and not having much of a hammer to hang over their heads if they skipped treatment resulted in significant failure. Time Magazine had an article on various city jails and parish prisons in the United States, and New Orleans' Parish Prison was voted among the top places to stay for food at that time. So, that study was a total flop, and it told me I'd better put my efforts elsewhere, that these patients were too far gone for us to step in and do treatment after they had been in jail 50 times or more.

TB: You mentioned the name of Jerry Levine, the successor of Jonathan Cole.

DG: We might have written something together for the Psychopharmacology Research Branch, but it slips my memory right now. Jerry was a good influence following Jon Cole. That was a very good selection and he continued doing some of the things Jon did, so he was a definite help to us.

TB: You also did some work with Leo Hollister.

DG: Yes, and with George Simpson we did some collaborative studies, and also with Arthur Sugerman. I think we also did one study with Sam Gershon, but I'm not sure.

TB: What did you do with Art Sugerman?

DG: I think it was one of the drug studies, because I know we became very friendly. It just slips my memory.

TB: Is there any other drug you worked with that you would like to mention?

DG: Thiothixene was a relatively good drug, because the sedation was much less than it was with some of the other antipsychotic drugs and its' EKG effects were practically nil. It was very clean in that area compared to Mellaril.

TB: You got interested in side effects very early and published extensively on them.

DG: Yes, I published also on the hematologic side effects of Serentil.

TB: Then you became involved with alcoholism and substance abuse. Didn't you direct a substance abuse center?

DG: I was Program Director for the southern part of the state from 1962 until I retired in1990. During that period of time, I was the only psychiatrist from Mandeville, on the other side of the lake from New Orleans. This sounds rather absurd, but I was responsible during those 30 years or so for almost 10,000 patients who came through our inpatient and outpatient program. And, one thing I'm proud of, probably the thing I should be most proud of; every one of those patients had my home phone number and my work number. I had a card I would give to every patient that came through our clinic or our inpatient program and to every patient that came through my VA program. I started that in 1985. Every patient knew they could call me anytime they wanted to.

TB: So, you were always available to your patients.

DG: The schizophrenic families or the patients themselves. This was very, very rewarding and it was very rare when a patient took advantage of it. Rather than tell a patient I was going to see them in a week, I would have them call me in two days and let me know what was happening. We might even increase their dosage in 3 or 4 days, not having to wait a week. So I was able to escalate the dosages more rapidly. It was very rewarding for me and the patients. The patients sometimes would almost go into shock when you gave them a card with your home phone and your work number, so it made for a very good automatic doctor-patient relationship to start off with. In fact, when I was doing the Fischer Project and running the free medical clinic, I was doing house calls. I wouldn't do that nowadays. This is back in 1969 through 1975 or so. Then, there were a lot of knives and only a few guns. Now, there are a lot of guns and a few knives. I would make house calls with the president of the TCA organization, an African-American. One time, the president came to see me and said, "My aunt just came down from Connecticut and she was in a mental hospital up there. Now, she's flipped out again. Can you come and see her? She's got a butcher knife in her hand." So, I said, "Yeah, but you're coming with me." So, we went into the apartment and there she is, holding up a huge butcher knife in her hand saying, "I'm going to be killing someone or kill myself because the voices are telling me to." She looked at me, I had my white coat on, and said, "Who are you?" and I said, "I'm a doctor". She answered, "You're no doctor; doctors don't make house calls." I cracked up and started laughing. Keith, the president, started laughing and she started laughing and put the knife down. That was a wonderful episode, a wonderful scene. I'll probably remember that on my deathbed. All of these things were very, very rewarding and that was the most fun part of what I was doing, so it was well worth it.

TB: It seems that you had numerous activities simultaneously.

DG: Yes, we were too far spread out. I sometimes think I should have devoted almost all of my time to psychopharm, and yet when I look back on my memories, I'm very happy I did all of that crazy stuff.

TB: Didn't you also study sexual behavior?

DG: That was a joke. I really didn't study that. What happened was that there was a magazine called Medical Aspects of Human Sexuality. I don't know why they called me to write two articles; I thought it was a joke, but they were offering to pay me $250.00 for an article on something I didn't know about so I said, great. One article was on Sexual Positions during Pregnancy. I thought I would play a joke. I went ahead and wrote that the best position is the pes caelum position, which meant "foot in the sky". The editor corrected it and changed it to "foot on the ceiling" and published it. They give me $250.00 for that. I thought, hey, this is a great occupation. That was a good deal of money for an academic back in the 1970's. I mean, you can publish anything you want in this magazine and get revenue. Then there was some other article, I've forgot what the title was, but I had one reference as something about "how to grow aphrodisiacs in your garden" by William Shakespeare. They published that in the Medical Aspects of Sexuality. I also worked with pipotiazine palmitate. Do you remember that?

TB: Yes, of course.

DG: A drug with a very long half-life. One injection lasted almost four weeks. I don't know why it never became commercialized in this country, but it worked very well in the chronic schizophrenic population. It was the first significantly long-acting neuroleptic. It was an ideal drug, once every three to four weeks. In my introduction to the study that we did, I wrote that this compound had such a long duration of action it must be slowly metabolized by the liver and would work well in people who had the "Simpson syndrome." In the next sentence I added in reference to the "Simpson syndrome" that the drug is only slowly metabolized in the liver when drinking "First Growth" wines. When I mentioned the "Simpson syndrome" in my presentation at the ECDEU meeting, everybody got a good chuckle out of it. I used that presentation to cite that as a reference in the article. It was a joke, but, it was fun at that time. I was somewhat of a mischievous character at times.

TB: When did you get involved with medical ethics?

DG: I must have had some guilt about my mischievous behavior. It was when Phil May was president of the ACNP back in 1973 or 1974, around that time. Phil was a fantastic person. He was the British version of Heinz Lehmann, very gracious, and if I remember correctly, he was

the first investigator to perform a comparison study of psychotherapy with drugs in schizophrenia. It was an early study and the design was chlorpromazine plus psychotherapy, vs. CPZ alone vs. psychotherapy alone.

TB: What did he find?

DG: Psychotherapy by itself was like placebo in those schizophrenic patients. In the early studies, chlorpromazine by itself is significantly better than psychotherapy in schizophrenics and psychotherapy added nothing to the efficacy of CPZ. That was really the conclusive study showing that all this nonsense by Brody and Redlich, the schizophrenogenic mother, and John Rosen, direct analysis, was useless. I was Chairman of the ACNP Ethics Committee, at that time and Phil asked me, since I was Chairman of the Ethics Committee, to start drawing up guidelines, stating the principles of Ethical Conduct for the ACNP. It took a lot of my time but I really got involved. In fact I asked Dave Mielke to take over as principal investigator of our ECDEU grant because I was spread too thin. I was overly involved in developing the Statement of Principles but I think it was the first Ethical Code developed for any medical organization. Psychology had their own, but not any medical or research organization I'm aware of. I spent about two years on that, working with Bob Force, a lawyer at the Tulane Law School, and the entire membership of the ACNP. I sent out several drafts to get input from every member and reviewed all of the inputs. Most of the members returned it so reviewing their comments and trying to incorporate them was a much greater job than I realized it would be. Since Phil May had asked me, I was obligated because I felt indebted to him as a person. He was just a fantastic individual. We finished it after about two years and it came to a vote by the membership. We had about 162 members at that time and only one member voted against it. I thought to myself, out of all these eccentric people who belonged to the ACNP, to have only one person vote against it was a fantastic accomplishment, so I was well satisfied. We modified it again in 1984-85, and it has been modified and changed quite a bit since that, as the years pass. That was a very intense piece of work and it made me examine a lot of what I was doing. It was very educational for me and I learned a lot. Bob Force and I later edited a book on Legal and Ethical Issues in Human Research and Treatment that had the Imprimatur of the ACNP. We had Albert Jonsen, Angela Holden from Yale, Alan Stone, Karen Lebacqz, Robert Levine and other contributors. Also Father McCormick at Georgetown was another person who was very sharp in this area. So, it exposed me to quite a few people outside our field and was something I can thank our

organization for, because I never would have got involved in that area, were it not for the ACNP.

TB: You also wrote several chapters in that book.

DG: It was a book on Ethical Informed Consent for Research and Treatment. I felt that was a complicated area for schizophrenics and still is.

TB: It was a very successful publication.

DG: Yes, we had a good number of reprint requests. In fact, there was a spin off. I was invited to a number of places to give lectures. It was unusual at that time to have the Principles of Research, which had some legal implications. I think the one person that voted against it was afraid of legal implications. I received invitations to participate in symposia in Michigan and in Boston. It exposed me to different areas and I became quite knowledgeable.

TB: You also wrote a book on alcoholism, didn't you?

DG: I wrote a book on alcoholism by myself. That was probably one of the things I did that required more time than anything else. It was "Early Diagnosis, Intervention and Treatment"; describing, not only diagnosis, but the various types of interventions and treatment modalities. Treating alcoholism is a difficult problem; the non-compliance rate is quite high but no different from asthma or high blood pressure. The idea that you have a genetic susceptibility for alcoholism as well as for high blood pressure, asthma, and diabetes, and comparing it in these terms makes it more acceptable as a chronic medical illness. I've also written on the relapse or non-compliance rate, showing that the rate in alcohol and drug addiction is not that much more significant than non-compliance in diabetes. In one survey of diabetics, where medication was prescribed by their physician, approximately 50 percent did not take their medication as prescribed. Pretty shocking, that it was almost as high as the non-compliance rate with alcohol and drug addicts. So, one relapse should not be regarded as an end-point any different than with diabetes or high blood pressure. About 50 percent of hypertensives don't take their medications, as prescribed, at one time or another. The worst case of non-compliance I use in teaching medical students was published in the Lancet 12 or 14 years ago on congenital hypothyroidism. Almost half the mothers were not giving thyroid as prescribed for the children. That is incredible. By trying to get people to understand non-compliance not being that different in alcoholics and drug addicts from other medical illnesses, I felt like I could make it more acceptable to the public and encourage less negative reactions which I always felt was very important. Psychiatry has always had a problem of acceptance in one way or another, lesser nowadays than years ago. When I

first told my friends I was going into psychiatry, my best friend stopped talking to me for two days. That's a true story. He said he was going into Internal Medicine and went up to Mt. Sinai and became an outstanding internist. He said to me, "You're leaving medicine; you're deserting us." So, psychiatry has had a tough row to hoe, as far as being accepted.

TB: North American psychiatry was almost entirely psychodynamic at the time you entered the field, but it seems that New Orleans with Heath were biologically oriented.

DG: Right.

TB: So, in a way, you were lucky.

DG: I was very lucky. He gave me a chance to get my feet on the ground and I can thank him for that.

TB: Were you involved in psychodynamic psychiatry at all?

DG: I wrote a little paper one time for GPs on how to treat primary care patients psychodynamically, but I'm a bigger fan of the systems they worked out in recent decades; interpersonal therapy, cognitive behavior therapy, and more recently, the cognitive behavior systematic analysis model for depression. I'm much more impressed by their results as they're easier to evaluate. I've read the Interpersonal Psychotherapy book by Weissman and Klerman, because I have to teach part of that to my residents and discuss it with them when they're seeing patients. When I retired in 1994, Tulane was very nice to me. Since I put in 40 years of teaching they made me Professor Emeritus and let me have an office across the hall and a secretary. I don't get paid. This way, I'm in control of my life, which was never true before. I come in three days a week, on Mondays, Tuesdays and Wednesdays, teaching medical students, the freshman, sophomores and juniors and the first year and second year psychiatry residents. The areas I cover with them are the psychopharmacology of anxiety, affective disorders and schizophrenia. I also teach group therapy techniques, and alcohol and drug abuse. Those are the main subjects. It keeps me feeling young working with young people, which is very, very important, so my marbles don't get too rusty!

TB: So, you do that three days a week?

DG: Yes.

TB: And, the rest?

DG: The rest of time I'm reading. I was accumulating books that had nothing to do with medicine for many years, looking forward to the day when I retired to read them. Nowadays I read more medical journals than I did before, because I didn't have time, but I also read more novels, both fiction and non-fiction. I have much more time to do that, because reading

is a major part of my life. The only problem I have is in my compulsiveness. When new books or magazines come out I don't have the ability to turn them down, whether they're medical, non-fiction or fiction books that have nothing to do with medicine. So I keep on buying books and magazines; for example, The New Yorker, Scientific American, The N.Y. Review of Books, etc. I've never caught up with all the books I've been saving to read in retirement. But I hope I never catch up. It's fun!

TB: So, you read a lot.

DG: I read an awful lot. I read more than ever before. I'm always calling up George Simpson to tell him about something I've read. He does that with me. He reads a lot, also.

TB: Do you keep close contact with George?

DG: Yes, I've always felt George and I had a lot in common in spite of our tremendously different backgrounds. We've always had fun with each other and I like to think that attracted us to each other as well as our interest in food.

TB: Good food.

DG: Yes, we both enjoy good food. That's one of the reasons I stayed in New Orleans. When I look around the country and think of different opportunities, such as Kansas City, oh my God! I couldn't handle that food, and my wife also enjoys good food, so we had no choice but to stay. And, it's a very interesting town. We live in an area that's only twelve minutes from downtown, and yet it's totally different from the French Quarter and the French Market.

TB: I remember when we had an ECDEU meeting here. I also remember the hospital you worked in those years. We were traveling for two and a half hours to get there. .

DG: Yes, but we have an interstate now. At the time we had the ECDEU meeting down here back in the 1960s we had a meal at Antoine's. Were you there?

TB: Yes. That was in 1967 or 1968.

DG: I asked each ECDEU member to chip in about $10.00 or $12.00. The wine we were served was a Chateau Pontet Canet. I remember because I had to pay for part of that wine out of my own pocket. Arnold Friedhoff got up at the end of the meal and toasted me, saying something about how fantastic. They got their money's worth and I was thinking to myself part of that was my money!

TB: Let me switch. Could you tell us something more about your involvement in group therapy?

DG: I enjoyed group therapy very much. I'm doing group therapy right now. We had a group therapy association, Louisiana Group Therapy

Association, as part of the National American Group Psychotherapy Association, and I was very involved in it. We had no one to teach us that in 1962 and 1963, so I used to meet with four or five prominent psychiatrists in town, one night a week. We'd supervise each other, criticizing each other and reporting on our groups. That was the only way we could learn because we had nobody to teach us. There was somebody named Hugh Mullan up in New York who worked with group therapy. He was very good so we had him down as a guest. I was enjoying it so much; working with alcohol and drug addicts, the group phenomenon naturally takes place. That's what some of us call the pseudo-cohesiveness, false feelings of togetherness when we first meet somebody who has the same background we do. Example: when I was overseas in the Air Force, in the Philippines, I hadn't met anybody from Brooklyn, New York in a couple of months, which is unusual, because we had a couple of million people living there. Then, one day, somebody came over to our Air Force base and I met him, another doctor. He was from Brooklyn and he went to the same high school I went to, Boy's High School. Before you know it, you start getting close to a person, even though you know nothing about them. That's what I call pseudo-cohesiveness, false feelings of togetherness. Of course, later on, about two or three months later, I found out he was a real terrible person and I didn't like him at all. So, sometimes our first impressions are not the right ones. But, in the beginning, alcoholics have this automatically happening to them. "Oh, you're an alcoholic; you go to AA. What AA group do you go to"? So, they fall, naturally, into this group phenomenon, and they're easy to treat with group therapy, much easier than other types of patients. Nowadays, most of them are mixed drug addicts and alcoholics, but they still have this AA approach or NA (Narcotics Anonymous) approach. I started to really enjoy group therapy because it flowed so smoothly and so evenly and we worked out some techniques that worked quite well. And, at the same time, I started realizing, early in treatment programs, that if you didn't deal with the spouse, you're missing out on a gigantic part of the patient's life and each one of us sees the world through our own eyes. The more eyes you have to help you see the world, the more valid the observations become. So, I started putting this practice into married-couples group therapy, treating six or seven couples at one time. I used to do this on Wednesday afternoons, two groups, one from 1:15 to 3:15 or 3:30 and the other one from 3:30 to about 5:30 or 5:45. They were coming from Baton Rouge, because I was the only one doing this for the state. They also came from Lafayette, Louisiana, Cajun country, and they were people

who were fun to deal with, especially the Cajun population. They love to drink and they love to talk, so they are very good patients. And, I found out that when we did a follow-up on the first 160 couples that we treated, back in 1969 or 1970, only two of them had separated in the eighteen month follow-up, which was probably below the national average. My success rate, as far as abstinence and decreased days of drinking, was much higher because that was a select population I was dealing with. Of course, if they're still married, that means they have a support system, and if they're still married, they're more likely to have a job, so you have more positive predictors working for you by just treating married couples. You have a much better chance of success. This added to my enjoyment, because I might have been finding failure in one area, but I was successful in this area; that made it much more fun. You need to have some positive reinforcement with a group that's difficult to treat.

TB: What about drug therapy?

DG: One of our former residents, Chuck O'Brien, showed naltrexone efficacy very nicely, along with Stephanie O'Malley from Yale. In two separate double-blind studies, they showed how naltrexone decreased the number of drinking days and decreases craving to some extent. The data are solid; two separate studies done without each one aware of each other, coming up with the same results was impressive proof of the drug's efficacy. So, we now use naltrexone frequently. One other thing I forgot; I used to consult on college campus two half days a week treating Tulane uptown college students. I started going on Tuesday afternoon and Friday afternoon, it must have been about 1973, which was a nice change of pace from drug abusers and schizophrenics. It was like ice cream, soda and candy, to consult and treat college students. They had a number of eating disorders. In bulimia cases, I used naltrexone, not in a research study design, but case by case, and had some good results with a few cases, decreasing the binge eating and euphoric responses to carbohydrates. At the same time, I had the opportunity to participate in a naltrexone nationwide VA study with Leo Hollister, who was on the committee to look at the data for using naltrexone with heroin. Of course, those were very disappointing data. The patients would stop taking it. With naltrexone in bulimics I had patients, when they graduated, who were afraid to leave town because they might not get the naltrexone elsewhere. So, it did help a sub-group of bulimics. But, I wasn't running a controlled study.

TB: So you were using naltrexone in bulimia. What about Antabuse (disulfiram) in alcoholics?

DG: I always used Antabuse, but I tried to get a support system to supply it to the patient. If there was a wife, I'd have the wife give the Antabuse to the patient. I would tell a patient, you're not taking it just for yourself; you're taking it for the family. If they didn't have a family and they were working, and had an employer, I'd have the employer give them the Antabuse. So, I tried to bring in support systems to administer the drug. Of course, the original Antabuse study with controls was done by Fuller, at Cleveland Clinic, before he joined the NIAAA. He did that in 1973 or 1974 and found no higher abstinence rate at the end of nine months, but he did find a significantly higher number of days of abstinence on the Antabuse. But the abstinence rate was only twenty percent or less in nine months. Just seeing that data, you automatically realize if you have a support system, use them to give the Antabuse with the patient's permission.

TB: What else were you involved with?

DG: Teaching and supervising. You have to be careful with Antabuse therapy in schizophrenics, because Antabuse does inhibit dopamine ß-hydroxylase, and you don't want to increase their dopamine too much. So, in schizophrenics, I would use a placebo dose of Antabuse, 125 mg/d. We did have a problem with our schizophrenics who were crack abusers; they had a little bit more of a response problem. I think George Simpson made some similar observations. Our patients would become more outgoing, their thought dissociations might decrease, but sometimes the paranoid delusions and hallucinations persisted. I found myself getting desperate and would add a small dose of a dopamine-D_2 blocker on top of the atypical antipsychotic, and, in some cases, the voices would go away. I haven't done a double-blind study, but I have a suspicion that the reason is that cocaine causes renal vasoconstriction with a decrease in blood flow velocity and vasoconstriction in the brain vessels resulting in decreased perfusion in the brain. Perhaps not all of our drugs are getting through to the right areas and these patients may need more of a kick with a dopamine-D_2 blocker in addition to atypicals. That's been an observation of mine and I think George agrees with me. The dual diagnosis patients we wrote about back in 1979 have increased, dramatically as the years go by. There are several good chemical reasons for that. I had an interesting experience about this problem. The original report on the incidence of alcohol and drug abuse in primary psychiatric patients came in 1975, or maybe a bit earlier, from the Bronx VA Hospital. The incidence was almost sixty percent in an urban psychiatric hospital. At Charity, we were running about the same percentage. In Wisconsin, they asked me to come up

there for a three day seminar on alcohol and drug abuse, about twelve or fourteen years ago. I was giving them the data about the incidence of dual diagnosis problems in our primary psychiatric patients and I made the statement, "I guess, here in Madison, Wisconsin, you're not going to have the high incidence, because you don't have that much of an intense urban situation". They were too polite to disagree with me but two weeks or a month later, I received a manuscript in the mail from a PhD psychiatric social worker with data showing me that the incidence of dual diagnosis in their study was about forty to fifty percent in primary psychiatric patients. So, it didn't seem to matter: wherever you live, you're going to have an increasingly high incidence. It's a real problem because it contaminates drug studies, particularly in outpatients it's a disaster. It was much easier to do studies years ago. There was a study done in New York State, I reported on for the Journal of Clinical and Experimental Research in Alcoholism about thirty years ago, on the incidence of depression, anxiety and schizophrenia among primary alcoholics. It was done in sixteen or seventeen different units in New York State. The incidence was only about ten percent. Nowadays, we see a much higher incidence of substance abuse problems in our primary psychiatric patients and vice versa. It's gotten much worse.

TB: Besides naltrexone and Antabuse did you use or study any other drug in alcoholics?

DG: We tried lithium, which turned out to be of no value. We did a lot of antidepressant studies in primary substance abusers, but we didn't do long-term follow-up to see if it had an effect on abstinence.

TB: You mentioned using SSRI's in alcoholics.

DG: The Toronto Addiction Research Center, which is one of the best on this continent, reported a short term study using one of the SSRI's in a one month study to decrease alcohol intake. This was some years ago, and because of their findings we tried it, but we didn't do an adequate double-blind controlled study. So I can't be objective. When you're doing double-blind studies in this population, you have to sort out those with major depressions and eliminate them just to see if a pure SSRI can reduce the alcohol intake.

TB: Do you have a preference for any antidepressant in alcoholics?

DG: I like short-acting compounds, so I would choose sertraline, something that's a little bit more pure as far as affecting the liver.

TB: What about doxepin?

DG: I would not use doxepin now with the SSRI's available. Cardiac wise, you're better off with SSRI drugs. Our alcoholic population seems to be more sensitive (now this is subjective), to anticholinergic side effects

than our non-alcoholic population. I have no idea why; it just seems that way. I have more complaints in that area. So, I tend toward the SSRI's for depression in these patients.

TB: Do you remember which antipsychotic drug you studied first?

DG: We might have done work with Stelazine, trifluoperazine. Then we used that as a comparison to a newer line of drugs in our studies.

TB: Which was the last antipsychotic you studied? Did you work with any of the atypical antipsychotics?

DG: No, I handed over the unit to Dave Mielke before the atypicals came out.

TB: When did you hand things over to Mielke?

DG: 1977, somewhere around that time, when I became overly involved in the ethics code and substance abuse.

TB: Didn't you work with penfluridol about that time?

DG: Penfluridol was one of the last the compounds I worked with. It was a beautiful medication in our patient population. We gave it orally once a week and it worked, as far as antipsychotic activity was concerned.

TB: There was a paper published recently on the effect of penfluridol on the EKG.

DG: Is it used in Europe?

TB: At a certain point in time, it was used very extensively, because it is a selective dopamine-D_2 blocker.

DG: The side effects were minimal. I had fantasies of using that compound and training a high school graduate to make house calls once a week on my schizophrenics, who were living at home or in a residential home, giving them the medication orally. Another compound, I worked with was sulpiride. That was a clean compound. We didn't find any side-effects to speak of in our chronic schizophrenic population, and it's quite an active antipsychotic compound. In Europe there were some controlled studies showing that it was also an antidepressant.

TB: When did you study sulpiride?

DG: That was about 1976. That might have been the last compound I did and thought was clean. I have no idea why that didn't go any further here.

TB: The benzamides are very successful in Europe, but they are not used in North America.

DG: I don't know why. They are cleaner than the atypicals.

TB: Did you work with clozapine?

DG: No, we didn't have that opportunity. Herb Meltzer was doing it in about 1980. But, sulpiride was another ideal drug. Sulpiride and penfluridol were two of the nicest drugs that came down the line but they didn't become commercial in this country. You mentioned the possibility of

EKG problems with penfluridol, which I'm not aware of, but that would be something to think about.

TB: Are you still using haloperidol extensively?

DG: No. I may use it every now and then; sometimes intravenously. For example, in a mentally retarded patient who had chewed off her fingers, while putting on a cast to protect her from further damage, we used intravenous haloperidol. Otherwise, I tend to use more atypicals. One reason for not using antipsychotics too quickly is that someone might come in with a PCP psychosis, which can look like schizophrenia, so the patient clears up after an antipsychotic and you will not find out what the basic problem was.

TB: You also studied withdrawal effects of neuroleptics, didn't you? You had a paper on that some time ago.

DG: I think that was one of the mistakes that we made. In one of our drug studies, with a phenothiazine derivative, for some reason we stopped the compound and had nausea as a result. I regarded that as a rebound phenomenon, but that was a mistake. George Simpson corrected me on that, because we had also suddenly stopped our antiparkinson drug. So it was really a rebound from the anticholinergic, a cholinergic response with nausea. I was a little embarrassed about that.

TB: What about antidepressants? Which was the first antidepressant you studied? Wasn't it desipramine?

DG: Yes, that was the first. We might have studied one or two other antidepressants that had a number, but were no better than placebo. In the beginning, when we arranged to do double blind studies on the Charity Hospital outpatients we were trying to concentrate on depression. We might have used one or two compounds in the beginning. Desipramine was the first real active compound we tested that had definite activity compared with placebo. It still is a very nice compound.

TB: Which was the last antidepressant you studied?

DG: I'm not sure.

TB: You have also been very involved with the benzodiazepines. Weren't you on a committee on the benzodiazepines?

DG: Yes, it was the APA committee.

TB: Would you like to comment on that?

DG: Carl Salzman was also on that committee and some others, of course. It was to evaluate the addiction and dependency problems of the benzodiazepines. The recommendation was that there were some people possibly more susceptible to addiction, but the overall opinion was these drugs could be handled comfortably if the patient had the correct diagnosis of Generalized Anxiety Disorder. Otherwise, there was an

addiction potential. But the data on the benzodiazepines was interesting in a sense; I had a run in with the manufacturers of alprazolam. When I was a member of the FDA advisory psychopharmacology committee, alprazolam (Xanax) had already been approved to treat Generalized Anxiety Disorder. I was given the assignment, by the FDA committee, to evaluate its antidepressant activity because the company wanted to market the drug and list it in the PDR as an antidepressant as well as an anti-anxiety agent. There was a suggestion to compare it with placebo. But, I had a great deal of concern, which I expressed in my report to the FDA psychopharmacology committee, that if alprazolam was listed in the PDR as a primary antidepressant, patients with depression were going to get addicted to the compound. They could be more susceptible due to the anxiety that accompanies depression. The data showed that it didn't seem to be as effective as our primary antidepressant medications. So, the company did give me somewhat of a hard time. Depressed patients with low self-esteem could be more liable to the potential addictive properties of benzos if there was an inadequate antidepressant response. It never did get approved as a primary antidepressant and I was happy to see that. I didn't think it was needed in that area. In our alcoholics, while we don't have any objective evidence, we do have some data that suggests alcoholics may be more susceptible to benzodiazepine addiction. Cirillo, in Boston, has published data on adult male children of adult male alcoholics using a euphoria rating scale, comparing 1 milligram of alprazolam vs. placebo. They scored significantly higher on the euphoria rating scale on the drug than they did on placebo. So, those suggestions make me a bit worried. I've seen benzodiazepines spread out too much across the world.

TB: During the years you were involved in clinical trials with psychotropic drugs major changes were taking place in the methodology of clinical investigations.

DG: When I was at NY Gowanda State Hospital in 1954, not only did they use insulin shock, they were also using ice cold baths. When I saw that I just went into shock myself. They had the patients tied who were agitated or sullen tied in restraints surrounded by ice bags. It was like a horror movie, I saw things that I shouldn't have seen. I was too young. I never did see a well-controlled study of insulin shock therapy.

TB: Do you remember when the BLIPS system was introduced?

DG: It was a tremendous addition to psychopharmacology evaluations, getting into objectivity. I used to brag that psychiatrists in the sixties were more objective in their drug evaluations as the BPRS and the BLIPS came along than internists and other medical specialists, even though

they gave psychiatrists a hard time for being so subjective. We were actually, more objective in what we were doing. And I felt good about that.

TB: At the time you started there were no ethics committees, no patient consent forms.

DG: We had to get patient consent at the East Louisiana State Hospital to move them onto the research unit. On the consent form it said that the patient would be receiving investigational drugs, that the families would be notified and if they had any objections, the family should tell us and we would give them the results. But, of course, these families were, for the most part, emotionally if not physically separated from the patients. A part of that, you might say, was hypocritical because we knew the families would not respond. And over ninety percent did not; ten percent did, I would say. We also had to obtain judicial consent from the local judge. So it was paperwork consent in a way. That's one of the things I questioned myself on, when I was doing the ACNP statement of principles. I questioned my own approach to research and that was a very healthy thing to do. With our alcoholics and drug addicts we always obtained consent from the patient, it was something we did without thinking, part of our routine. But it wasn't as good as informed consent is now. It wasn't as detailed, but the patients were told that at one time or another they might not be receiving active medication. We also told them about the potential risks and benefits. I don't ever remember doing a study without a written consent.

TB: So, you did have signed written consents from the beginning?

DG: What happened was that because of the type of research Heath was doing, which had some real dangers, putting electrodes into the brain, he had to develop a consent sheet at the medical school's insistence. That might have had some spin-off effect in psychopharm so that, automatically, consent sheets were expected, not by the department but by the medical school.

TB: Were you the one who implemented the program in alcoholism in Tulane. You ran it for well over twenty-five or thirty years?

DG: I didn't implement it, but somebody who was vice president of a prominent clothing store. He had a brother, who was an alcoholic.

TB: When was that?

DG: This was 1961, and he had a lot of influence in the State legislature so there was a building built for student nurses at the psychiatric hospital in Mandeville on the very large beautiful grounds; this building was to house the student nurses while they rotated through their training. The contract fell through at the nursing school leaving this beautiful building

empty. It was the perfect place for treating alcoholics and drug addicts. There were thirty-two beds, males on one side, females on the other side, no more than two patients to a room, private bathrooms. It was one-story, when they walked out of their rooms, there were the piney woods, and it was just unbelievable. But it all happened by accident; nothing like this is ever planned. Often you plan something and it turns out horrible. He was able to get that building and get the funding to run the program; his name was Simon Marx. I remember him well, a big, hefty man who was very outgoing and knew what he wanted. So, I had this building and state funding; it was a part-time civil service job, which helped a lot. I was only making twelve thousand dollars a year with my psychopharmacology grant, and I needed extra money for my family. This was a part-time job that helped me financially, because I never did enter private practice.

TB: So, you were never in private practice?

DG: No.

TB: But, then, you ran this program until when?

DG: 1998; when I retired from this area.

TB: Can you tell us something about the program?

DG: The Alcohol and Drug Treatment Center?

TB: Yes.

DG: I had a lot of emotional investment in that; because of the staff and the patients I did a number of things with the program that nobody else does. Because of my time limitations, I was there just two days a week. On Monday from twelve noon until five o'clock, and on Thursday morning about five-thirty a.m. We would wake up the poor patients early. It was a terrible thing for me to do to them. I then left at 1 p.m. for Tulane. Within that limited period of time, I did a lot of things. I had to run ward meetings twice a week. But I'd have the nurse call me every day at home in the evening and make ward rounds on the phone, one patient at a time. If the patient had to talk to me, I'd talk on the phone. I used the phone an awful lot. Either the patients would call me or the hospital would call to do ward rounds. When I went to the unit, I would do group staffing. Instead of staffing patients, one at a time, I'd staff three patients and have them interact with each other. I called it a group staffing procedure, which I published. That meeting would last for about two and a half hours, three patients at one time for three hours, rather than on one patient for an hour and a half each. I got them to interact with each other and it became an accepted routine. Patients are interesting, very fascinating. You'd think they'd be too embarrassed to talk about their problems. We would talk before hand about any sexual or

personal problems they wanted to discuss in private. The medical students, four or five at a time, would sit in with me as it was an excellent learning experience. We did a group family session, later on that day, with three or four families at one time, going over the history, getting the information, and so forth. It was a very intense treatment and the patients made good progress through this group process. The follow-up would be in married couples' or regular group therapy. Then we had the ward meetings, which I would do Mondays and Thursdays, plus the phone rounds. I had some excellent counselors I trained, who did a lot of behavioral work, including implosion therapy, and desensitization for social phobia problems, like fear of heights. When you do surveys the incidence of phobias is sky high in this population, but you don't find out unless you ask specifically. We used an eighty-two items Fear survey questionnaire, trying to make sure we didn't miss any phobias. We also standardized a relapse prevention inventory, (RPI), that I read about in Lancet to prevent relapse. And, we did a lot of role-playing, in addition to the group therapy and individual counseling. I'd have my social worker take the patient up to the top of the Trademart tower, step by step, for desensitization or all at once, implosion therapy, keep them looking over the side of the building until panic subsided, and then feed them a candy bar or ice cream as positive reinforcement. It worked but you had to keep them trusting you and stay with them, looking down from the top of the building. So we did a lot of behavioral work, in addition to individual and group work. I also used Antabuse in my alcoholics about ninety percent of the time. If they were married, the spouse gave it to them. If they were crack addicts, I automatically talked to them about Antabuse, because there was a study done in Arizona that even if those crack addicts who were not alcoholics drink socially, they were about seven times more likely to relapse compared to other crack addicts who didn't drink at all. Because of that, I tried to give it to crack addicts, and would say, "Antabuse might be an additional safeguard here." It's even more interesting since Chuck O'Brien published on the ability of Antabuse to elevate the cocaine level and cause uncomfortable symptoms in crack addicts. Some crack addicts were really highly motivated to take Antabuse, even though they weren't alcoholics. Very interesting! We had our dual diagnosis patients at VA, when I was running that unit from 1985 to 1998. In that program, we had a separate dual diagnosis group going on. In group therapy with dual diagnosis patients, we were a little bit more didactic, a little bit more educational and less confrontational. You don't hit the denial mechanism as hard. You've got to provide some social outlets for them to want to give up

their alcohol and drug abuse. You have to go slowly and tolerate more relapses with them, particularly in the beginning of therapy.

TB: During the years you worked with many people. Could you tell us something more about Mel Bishop?

DG: Mel Bishop, of all the people I worked with, was the most helpful and the most valuable, because he taught me a lot. He was a very retiring person who didn't come on assertively and he was very intelligent.

TB: Didn't he move to the pharmaceutical industry?

DG: Lederle pharmaceutical gave him a very good offer financially. The salary of a psychologist just wasn't high enough and Mel had four children. Some of them were already grown. They were going to college and he needed the money so he went to Lederle. Harriet Kiltie is the one who hired him away from us. Bill Swanson took his place, later on. Swanson was a sociologist-psychologist who could handle statistics.

TB: I have not heard about Mel for a long time.

DG: Shortly after he retired from Lederle, he developed bladder cancer. In fact, I wrote Mel's obituary for the Neuropsychopharmacology Journal. He died about a year and a half ago in Texas. He retired there to play golf. His son is a professional golfer, teaches golf at the course in Austin.

TB: So Mel was replaced by?

DG: Bill Swanson came along. But, Dave Mielke took over. Bill Davis is the other person who's extremely helpful. Dave ended up doing more of the evaluations in Jackson; I was doing less, having become involved in the alcohol, drug abuse and poverty areas while also teaching medical students.

TB: When you say you got involved in the poverty area, what do you mean? What did you do?

DG: It was a free clinic I started in the Fisher project, working with children in the Treme' area, getting those with the high absentee rate to school. The Fisher project work went on for about four or five years and we provided a free general medical service there. When they ended up getting a medical clinic established we were able to leave. I felt we had done our job and now they had a State clinic that could take over the medical responsibility for the area. I had seen about two or three thousand patients in the Veterans Administration program and over ten thousand in the State program, over the course of about thirty years. I'd been the only the psychiatrist in the Southern state program in Substance Abuse and I was the only doctor for awhile, until we got an internist to help out in the clinic. But, I had no physician on my unit at the hospital in Mandeville, except myself, part-time, so, we saw this

tremendous number of patients that I had the opportunity to treat and get involved with. I'm always running into them wherever I go. Without naming restaurants, there are one or two I go to, where about one-third of the staff were patients of mine at one time or another. It's a very interesting experience, to say the least. I have a cute story to tell you. This involves Dave Mielke and me. Dave and I, while we were working together, running the psychopharmacology research unit, would occasionally have dinner at Antoine's Restaurant in New Orleans. Also, when we had guests in town, we sometimes would go there. Sometimes Dave would take a guest; sometimes I would take a guest, sort of share the responsibilities. One waiter knew us very, very well, and had been a patient of mine, in the alcohol and drug unit. And, he'd done well. He had been sober now for about ten years or so, and working at Antoine's for about forty-five or fifty years. One Monday, we found he'd had a stroke and they put him in Tulane Medical Center, so Dave and I went to visit him. I thought he was comatose and I stuck him with a pin but he didn't respond and his reflexes were very hypoactive. I thought, oh, my God, this doesn't look good. Dave was standing on one side of the bed and I was standing on the other when I said to Dave, "Gee, who are we going to get as a waiter tonight?" Suddenly, now this is the truth, this fellow sat up and said, "What are you talking about. I'm still your waiter." It must have been an ischemic episode, not a stroke. So, I've had some fun with patients like that. Want another good story?

TB: Yes, please.

DG: OK, this is a true story. It doesn't sound true, but I had this bipolar patient, a shoe salesman who was an alcoholic. This was at an ACNP meeting in the seventies. I had a paper to present at one of the group meetings on the day after I arrived by plane. My wife was going to come with me. The day we were supposed to leave, our kitchen burns down from a grease fire, so she had to stay behind to take care of the insurance, but I had to go because I had this paper to present. When I was in the hotel, taking a shower that night the phone rings. My wife gets on the phone. She says, "Where are the insurance papers? I can't find them". So, I got out of the shower thinking, about where the insurance papers are; the operator gets on the phone and she says, Dr. Gallant, you have an emergency phone call from the States. It's one of your patients. So, my wife, being a good doctor's wife, said, "I'll hang up and call me back later". So, she hangs up. This bipolar patient, who relapsed, is drinking and he's drunk. He says, in his slurred speech, "Dr. Gallant how can I thank you? You've cured me and I've been able to sell three thousand pairs of shoes this week". I got so upset, so aggravated

that I hung up the phone. I had a bar of soap with me and I flushed it down the toilet instead of putting it back in the shower, I was so turned around. Sometimes, these situations are not that funny at the time; there's nothing worse than a bipolar patient who relapses on alcohol. They can drive you nuts, unbelievable. If you live long enough, you've had a good number of unusual as well as humorous experiences.

TB: You served on many committees during your career.

DG: The FDA Psychopharmacology Drug Advisory Committee was an excellent learning experience. One of our former residents, Linda Kessle asked me if I would join their committee. She's now in private practice in Washington, and her daughter came to be one of my Tulane medical students. That's when you know you're getting old! Being on the FDA committee was really educational. I had one time when I really got stuck, beside that aprazolam incident. I was one of the advisors serving as the Chairman of that meeting that day to evaluate LSD to be approved by FDA as an investigational drug. Without mentioning any names a former ECDEU person brought patients from his alcoholism unit in Maryland. And he had them parade before our committee, each one who had taken LSD, raving about how wonderful it was and how the drug cured them of their alcoholism. I had to sit there and moderate this meeting. He had no control data, no objective evaluations, and he wanted us to consider it as an investigational drug for controlled research. That was a learning experience, but it wasn't a very happy one. It was a day long session that was totally a waste. There's also another story I can tell you about LSD when I almost got thrown in jail. This took place here in New Orleans. There was a fellow in the French Quarter who was caught with about 3,000 tablets of LSD on him and about $5,000 in cash. He claimed that he was a spiritual leader for a religion called, the "League for Spiritual Discovery" using LSD. That, believe it or not, made it a constitutional case, due to religion. So, it ended up in the Federal courtroom, which is directly across the street from our alcoholism clinic. At that time our alcohol and drug clinic was located in the middle of the French Quarter, near the Royal Orleans Hotel. The Federal Courts were located directly across the street from us. The assistant district attorney, a woman, whom I dislike to this day, called me up and wanted me to testify, because we had done some research with LSD, which I didn't mention to you. I'll go back a little bit. We had what was called, a "head clinic" in New Orleans. This was during the "hippie days" and the Vietnam War. The kids were transients. So we had a "head clinic", which was a free clinic in the French Quarter. We had our medical students working there to treat the kids' medical

and drug problems. So, we had a good supply of kids who had taken LSD to do research with. Roberto Guerrero-Figueroa, and I took forty kids who had experimented with LSD twenty times or more. One group had flashbacks. It was two to three months after they stopped taking LSD, as far as we could tell. The other group had no flashbacks at all. Their use of other drugs seemed to be about the same, so the only difference between the two groups was that one had flashbacks and one didn't. We did all-night sleep EEG's on our research unit at Mandeville and Roberto, who was an excellent electro-physiologist, did the all night EEG readings. We didn't have computers set up then, so this was a time consuming experiment. In the end, we saw a much higher incidence of temporal lobe spiking from the scalp in the kids who had flashbacks, compared to those that didn't. It was about 60 percent vs. 15 percent, something like that. We published the data in one of the EEG Laboratory Journals. Anyway, this assistant federal DA found out about it and wanted me to testify in the case of the "League for Spiritual Discovery". So, I said, "Look, I can't do it right now. I have to go to Washington". Probably, it was an ECDEU meeting. I said, "We'll meet with you, now, in our office. I'll give you a couple of hours and tell you all I know about LSD". She wanted to prove LSD caused fetal abnormalities. I couldn't give her that data, because we didn't have any. I did tell her about the flashbacks on our EEG data and I spent a couple of hours with her. When I reached Washington, my wife calls me on the phone and she says, "You have a subpoena to be in Federal Court on Wednesday". I said, "Wednesday, after I spent time with her, she promised I wouldn't have to go to court and Wednesday afternoon is my married couples group therapy at the clinic and I have two groups to run from 1:00 till about 5:30 or quarter till 6:00". So, I said, "You know, I'm going to ignore the subpoena, because I gave her the time". So, that Wednesday afternoon, I was in the clinic. My 14 year-old daughter wanted to sit with me in married couples group therapy to see what it was like, because she was thinking about becoming a psychiatric social worker. I asked the patients if it was alright and they said, fine. She was really a sharp kid. So she was sitting with me in the married-couples therapy and handling herself fairly comfortably. In the middle of group therapy, my secretary gets a phone call from the Federal Court, across the street, saying Dr. Gallant is supposed to be in the courtroom right now to testify in this case. The court case is written up in these red brochures, US Court of Appeals for the Fifth Circuit No. 72-2464. I said to the secretary, "No, you tell them that I've got this group and that I gave the deposition." She said, "The judge says

he's going to send six Federal marshals across the street and carry you into the courtroom". I said, "Come on, now, you're kidding", hung up and went back to doing group therapy. About twenty minutes later, my secretary calls me again, she says, "They said if you're not there in five minutes, they're coming over here". I said, "Now, you're pulling my leg; don't joke around; come on, they're not coming here". Five minutes later, these six big hulking Federal marshals, and they were big, came in and picked me up, physically. My daughter is yelling, "Put my daddy down," and they carried me across the street to the Federal courtroom to testify in this case. I said, "Look, put me down, please, I've got to write some prescriptions for my patients". Some of them came from Lafayette, Louisiana. They did me put down and I wrote some prescriptions and, then, they escorted me, three on each side, across the street, my daughter following behind, yelling, "Let my daddy go". I walk into the courtroom. There are fifty hippies, probably hadn't bathed in five years. The courtroom was very smelly. They're sitting on the floor. They refused to sit on the benches, because that would be recognizing the Federal government. The spiritual leader, with this big long, red beard and shaggy red hair, was sitting with his attorney and the judge is yelling at me, not at the kids sitting on the floor, for not being there on time. When I try to explain that I gave a deposition, he wouldn't listen to a word I said. He said, "You just answer the questions. One more word out of you, I'll throw you in jail". OK. I'm sitting there testifying. Every time I testified with something that may be good for the defense, these kids started clapping. Every time I testified something negative, they'd boo me. The judge is banging away. It's like a B movie, comedy. The judge is banging away on the desk. My daughter is making faces at the judge for going after daddy, and I'm sitting there scared that I'm going to get thrown in jail. I've had so many things like that happen over the years. If you live long enough, you see a lot! Anyway, he didn't throw me in jail. The assistant DA won the case, but I never forgave her; she wrote it up in such a way that she doesn't mention my testimony as far as what happened in the courtroom. I was trying to tell the judge how she lied and betrayed my confidence in her, and the time that I gave her.

TB: Did you do any other research with LSD?

DG: That was the only time. I didn't work with LSD but I knew those who did. Heath and Russ Monroe worked with LSD when I was a medical student. Some government agency was concerned, in 1952 or 1953. They were concerned about the Chinese Communists brainwashing our prisoners of war and they had Ewen Cameron of Canada evaluating LSD, without informed consent, by the way. Do you remember that?

TB: I was working with Cameron on that project.

DG: Heath worked with a person down here, evaluating LSD and Russ Monroe did some of that work. They were also doing it without real informed consent, because that was part of the idea. The whole thing was crazy. Part of the idea was you're not supposed to know you're getting LSD if you're going to be brainwashed. So, they were only told they were getting some type of new drug, but there was no informed consent to speak of. This girl in my class volunteered for it. She ended up flipping out and had to be hospitalized for a couple of days. That was a terrible situation as far as LSD was concerned.

TB: During those years, people used LSD in the treatment of alcoholics. Did you use LSD in treatment?

DG: No, no. After I oversaw this FDA episode with the patient's parading in front of me, that they were into a religion with LSD, I thought this would not make for a good double-blind controlled study.

TB: Let us recapitulate briefly some of the events in your life. You moved to Tulane when you were eighteen.

DG: Seventeen going on eighteen.

TB: Started studying physics. Got a BS, right?

DG: I got a BS. in physics, and, actually, at that point, I applied to medical school and was accepted. They thought my physics major was a little bit unusual. They liked to take people who had biology and chemistry, and they were leaning to accepting applicants with majors in chemistry, biology and psychology but not physics. But I was a made a member of Sigma Pi Sigma, the Honorary Physics Society. I think that helped get into Tulane; otherwise, I don't know if they would have evaluated my application in a favorable way, because they were really very hesitant to take Physics majors. They felt that physics majors were not that interested in medicine, per se. That was a feeling I had and I was concerned when I applied, but it worked out okay.

TB: Your first paper was on dextroamphetamine if I remember well. When did you publish your last paper so far?

DG: This year. Well, not a paper, a chapter. Marc Galanter at NYU asked me to do this chapter on *Treatment of Substance Abuse Disorders* for the textbook that the APA puts out, and, then, Gabbard in Texas asked me to modify the chapter I did for this 2001 book on the APA *Treatment of Psychiatric Disorders*. So, I'm still, occasionally, writing.

TB: What else did you publish recently?

DG: That's about it. I presented on Dual Diagnosis and that kind of material at USC, George Simpson's place, but I do very little of that now, because I feel like I'm out of the research mainstream. I do keep up with

the reading, so I'm okay for doing reviews, but I'm certainly not doing any clinical investigations.

TB: Did you do any research after you retired?

DG: In the VA Hospital, we were still doing various types of studies, for example the study on urine drug screens, immediate feedback vs. delayed feedback, as far as treatment results are concerned. We published that data. So, I did a little bit later on, but not much.

TB: We talked about some of your collaborators. You trained many people during those years. Would you like to mention some by name?

DG: Steve Paul wrote his first paper with my supervision.

TB: Was Steve Paul your resident?

DG: No, he was a medical student. Steve wrote his first paper when he was a Tulane medical student and he started residency in Chicago with Danny Freedman. He wrote two papers with us. He asked if he could try one of the atropine-like compounds in our schizophrenic population and I told him to do a protocol for review and go ahead. Then, Earl Usdin asked me to do a chapter on cardiac effects of various psychopharmacological compounds and I asked him, "Look, I've got this medical student, who is very, very sharp. How about his doing the paper and being the first author? Of course, he's just a medical student and if he gets a lead authorship, even on a chapter, it'd be a nice start for him". So Earl Usdin said okay. The first time I think they had said okay for a medical student to do a chapter in a book like that. I told Steve, "Look, why don't you write the chapter? You'll be lead author. I'll go over the paper with you to correct anything, but this is your baby and that's it". So, he did it, did a good job.

TB: Have you kept contact with him?

DG: I was best man at his wedding. It was just Steve, his bride and me, my wife, daughter and the rabbi. They got married here in New Orleans. And, then Chuck O'Brien was one of our residents. He got his MD and PhD in Pharmacology down here and then started a residency down here. Peter Rabins, head of Geriatric Psychiatry and Vice-Chair at Johns Hopkins also wrote his first paper with me when he was a medical student.

TB: Chuck was President of ACNP.

DG: Right, so Chuck, Peter Rabins and Steve Paul were three of our successes, not bad, very good. We had some other good people come out of here. I was just thinking of a person the other day. One of them is on the faculty over at Minnesota. We had a couple of people ended up as academic successes.

TB: What would you consider your most important contribution to the field?

DG: I don't think I really made any significant contributions, when you really add things up. The things I hold as my contribution really didn't make any impact, like the idea of doxepin, in a controlled evaluation, being an anxiolytic back in 1969. I feel the times I served on committees, writing the Code of Principles, even though it's no longer applicable, was a very important thing. It was important for the ACNP to have one and important for me to do it; and it was very valuable at the time, particularly in being able to get the entire membership, with the exception of one member, to vote for it. That was a worthwhile accomplishment. Our controlled research with criminal alcoholics, first to report on trifluperidol, my teaching awards and the outstanding researchers I mentored. Steve Paul just wrote that I am on the "top of his list for making his career possible".

TB: Any other contribution you would like to mention?

DG: I think my contribution to all of my patients was probably more important in the long run, the idea of being accessible by home phone and cell phone throughout all these years. My main source of pride is having been always available to my patients twenty-four hours a day, seven days a week, even though it involved thousands and thousands of patients. When I think about anything important, I always think about that.

TB: I think those clinics in the poverty areas that you established were a major contribution.

DG: I felt good about that, although, there were some depressing episodes, you know. I mentioned the methadone patients, who didn't want to move out of the area, despite the fact that we would pay for their expenses. I think that the job we did with the children, taking them to school; things like that affected me more in the long run than some of the drug studies I did, which didn't take any great intelligence. Although, I should emphasize that we designed our own protocols, did our own evaluations and statistics. The only thing the pharmaceutical firm did was give us the drug. Quite different at the present time!

TB: Have you ever been involved with geriatrics?

DG: Only in my getting old, as far as my own particular aging process is concerned. It's kind of funny, I haven't thought about this in years. I did do some, back in about 1974 or 1975. An internist in town started a small geriatric clinic on Tulane Avenue, right by the Broad Street Police Station, and he asked me to consult with him, which I did for one year, to help him get it started. I did do it for a year, a half a day a week, just to get things started, evaluating the patients as far as organicity was concerned. That's why I was so happy I started off with neurology, that

gave me an appreciation for the organic aspects, not just the psychiatric model. After one year, I told him that was it. So, I did have that contact, which I'd forgotten.

TB: You received several awards and recognitions. You are a recipient of the Gold Achievement Award from the American Psychiatric Association.

DG: That was the best one, because it was twenty-five years of work. We had to submit all the research data we accomplished on the unit. We had to submit the number of patients we'd treated, the way we treated them, the whole program. I even enclosed my card with my home phone number and my work number to show how we did it. The only time I ever cried at an academic award was during that particular presentation, because it was twenty-five years of work.

TB: Then you also received the Gloria P. Walsh award.

DG: That's a very nice award to get from the medical school because it's for the entire medical school, not just the department of psychiatry and neurology, for teacher of the year.

TB: You received that for teaching.

DG: Right.

TB: You also had an award from the Association of Medical Educators. It was on substance abuse.

DG: Yeah, that also was a nice award, because the year before they gave it to Charles Leiber. Charles Leiber is a man I look up to tremendously, as far as research is concerned. He got the award one year and I got it the next year. So, in my acceptance speech, which they published in their journal, I talked more about Charles Leiber than myself.

TB: Then, you had the Robert Lancaster award.

DG: The Lancaster award had a lot to do with my community work. They recognized some of the clinical research but they had heard about the work I did in the poverty and alcohol and drug abuse areas with the State programs and so forth. So that was more of a community situation. That was gratifying.

TB: Then, for fifteen years, every year, you had awards for outstanding teaching.

DG: That's for outstanding teaching within the particular year so it's not as nice as the Gloria P. Walsh award. But it's a nice award because they have a banquet, you get up and they applaud. Very rewarding, the students and residents sort of keep me on the young side, because I know what's going on with the younger generation. And, I know any teaching time I put in is appreciated, particularly nowadays, because of the way medical school problems have developed as far as not getting paid for teaching hours. Volunteers like me are more valuable than they were

twenty or thirty years ago. In fact, I think we should end this interview with something Heinz Lehmann said. Before Heinz died, he was interviewed. I've forgot what journal it was; maybe it was mentioned in his obituary for the Neuropsychopharmacology Journal. He was working with New York State and involved in teaching until very recently. He said something like, I'm paraphrasing, not quoting; people over the age of 65 should pay to teach; not only should we teach for nothing but we should pay to teach. I agree, because I get much more out of teaching than the students or the residents.

TB: And these days you are reading a lot?

DG: I read anything that has a half way decent review. I use the New York Review of Books and the New York Times book section, the reader's section, and I listen to my friends, listen to George Simpson. He's turned me on to a few good books; I buy the books and, after I read them, I give them away. My wife reads them; I read them; we give them away, because I don't want to accumulate them. We pass them on to the residents or sometimes the medical students appreciate them. And, I read fiction and non-fiction. It doesn't matter. Books like *Regeneration,* Pat Barker's trilogy, are fascinating, a combination of psychiatry and a novelistic approach. In *Regeneration,* she talked about the poets, Siegfried Sassoon and Wilfred Owen, the greatest war poet who ever lived, in my opinion. They had a type of post-traumatic stress disorder and were treated by a psychologist who wrote the essentials up in Lancet in 1919. Pat Barker found out about this article and turned it into a novel. Fantastic, the best of the three books in the trilogy. I recommend it.

TB: What do you think about the progress made in the field?

DG: I think psychopharmacology is going in a beautiful direction. It's getting more and more specific with its drugs and they're hitting their targets much more accurately and the methods they have nowadays make the old time animal behavioral models looks so gross, it's pitiful. Yeah, I think it's fantastic.

TB: Are you pleased with developments on the clinical side?

DG: No, clinically, no. Of course, that goes for all of us, the HMO's, the PPO's, the whole thing is one big disgusting situation. I used to give out my home phone number to everyone. But, when a doctor gives out his phone number nowadays, the patients almost die from shock. Because of time restrictions psychiatrists who work at the hospitals, most of what they do is dispensing drugs. There's very little relating going on now between the patient and doctor and you can't afford it, financially. Let me tell you one story. Then I should let you go. One of our outstanding

residents, an excellent resident, he went to Seattle, Washington, after residency. He really enjoyed psychiatry. He really enjoyed people. He enjoyed relating, was very good with psychotherapy and psychiatric drugs and going to be an outstanding psychiatrist. Well, he didn't have much money, so he signed up to work in an HMO. The HMO decided he'll be, mainly, a drug dispenser. If the patient needs psychotherapy, he'll be seen by a social worker or a psychologist, which is less expensive. He had signed a three year contract. For three years he was nothing but a medication dispenser. That kind of story really is terrible. In medicine, in general, things are not the way they were years ago. You do find many good doctors, but as a group, they don't have time to spend with their patients.

TB: What would you like to see happen in the future in the practice of medicine?

DG: I would like to see that physicians, in general, have the final say as to how the patient should be treated and not have so many administrators make medical decisions. I signed up with an Insurance evaluation advisory group to find out the way they assess how long a patient should stay in the hospital. This group works for companies that insure patients for hospitalization and so forth. The insurance companies use groups like these to say if the patient is kept in the hospital too long. I joined up, not to do the work, but I was interested in learning. I spent my own money, making them think I was interested in joining, and went to Madison, Wisconsin where this particular group has its headquarters. I sat in on their two day meeting and realized their purpose is never to go ahead and extend hospitalization for somebody with severe depression, who might need it, and has too many residual symptoms for discharge, but the whole purpose is to cut down the hospitalization. Some of the ways they did this were obvious. Although the patients required additional hospitalization, they found reasons to cut it down or not to approve the days. Having experienced that was a good experience, I learned a little. This is not the way medicine should go. To evaluate patient stay, first, there is the local person, who is not a physician, but a nurse practitioner or someone like that. Then, it goes to this peer review, which has never even seen the patient. They're in Madison or in LA, but they're not with the patient yet they're giving second opinions, if there's an appeal. That is totally unacceptable.

TB: Is there anything you would like to see in psychopharmacology and especially pharmacotherapy with psychotropics?

DG: Treatments are becoming more specific. Researchers are getting down to receptors and genotype structures. For example, with the

benzodiazepines, they're down to the alpha sub units of the receptor. That seems to be more specific. In substance abuse, they are down to the behavioral trait of impulsivity associated with dopamine-D_2 deficiency receptors in the nucleus accumbens and even the possible IAI Taq gene for treatment choices. This is the type of research that will be extending to all areas of psychiatric illness.

More importantly, I would like to see the next presidential administration re-establish something along the ECDEU units with federal funding of independent academic, medical school institutions to do well-designed, reliable, honest, well-controlled drug studies with no impact or pressure from the pharmaceutical industry, whose only role should be innovating and supplying the new medications.

Most importantly, like all of us, I would like to see everyone have free access to good medical care if they are unable to afford it.

TB: I think on this note we should conclude this interview with Dr. Donald Gallant. . I would like to thank you Don for sharing all this information with us.

DG: You're welcome. It's been most enjoyable.

TB: Thank you.

GEORGE GARDOS

Interviewed by Thomas A. Ban
San Juan, Puerto Rico, December 9, 2003

TB: This will be an interview with Dr. George Gardos* for the archives of the American College of Neuropsychopharmacology. It is December 9, 1993. We are at the annual meeting at the college in San Juan, Puerto Rico. I am Thomas Ban. Let us just start from the very beginning: where and when were you born? Say something about your background and so on.

GG: Thank you very much for asking me to do this. It is sort of a celebration. It reminds me of a few months ago, my father-in-law invited a lot of people to unveil his tombstone in the cemetery and he brought champagne and everyone drank to the event. It's very nice that I can do this while I'm still around here and working. Let me say a few things about myself.

I was born in Hungary in 1938 and managed to get through the war. I stayed in Hungary and completed my high school and just when that happened, the 1956 revolution occurred. That gave a window of opportunity to people who were shackled by the communist system to get out. So even though I started medical school in 1956, together with another quarter million or so Hungarians I managed to get out to the West. I ended up in London, England where I had family. That is where I went to medical school at St. Bartholomew's Hospital, which is part of the University of London and where I got my medical degree in 1962. Interestingly, while in medical school I had practically no exposure to psychiatry, which was a deficiency of the English system then and probably of medical curricula elsewhere in those years. I recall walking up to the common room in the hospital where I would relax and play cards, to pass a lab of a Dr. Michael Pare. It was several years later I discovered he was doing pioneering work with MAO inhibitors. The other funny memory I have is that there was a pharmacology exam I would have done well on if, in the oral exam, I hadn't been asked whether I'd heard of chlorpromazine. I had absolutely no idea what it was for. The examiner explained it to me and I nodded wisely. Then, I forgot all about it!

After I graduated from med school, I spent a year in Rhodesia trying to figure out which way I was going. I was the assistant to a neurosurgeon, Lawrence Levy, there. He was the first important influence on my research career. He was busy with his practice, but he was also

* George Gardos was born in Budapest, Hungary in 1938.

interested in doing research, some animal experiments. So he encouraged me to make clinical observations and follow them up. My first paper was published while I was still in Rhodesia, which is now called Zimbabwe. It had to do with two cases of subdural hematoma resulting from anticoagulant therapy. My chief encouraged me to write it up and helped me with it. So it got published in the Central African Journal of Medicine. That taught me the importance of making clinical observations and, if they were of value, to communicate them in a publication. I also learned in Rhodesia that I was not cut out for surgery. From Rhodesia I came to the United States as a graduate student in psychology. I had an interest in mental health and ended up in psychiatry through the back door. As a graduate student in experimental psychology I got my masters degree.

TB: What was your master's thesis on?

GG: My thesis dealt with ability to rearrange the auditory environment. The subjects in my experiments were wearing "artificial ears" which deflected the direction of sound so that it appeared to be coming from the side, creating a conflict in determining where the sound came from. It was a way of studying plasticity in the nervous system.

TB: When was this?

GG: This was in 1965 and unfortunately my student visa was about to expire. So, I was headed back to England, but before leaving I took a trip to the West Coast to look around. On returning from the West Coast, just before starting to pack, I found out about a job opportunity for a research associate at the Massachusetts Mental Health Center with Al DiMascio. He was the next major influence in my career. He interviewed me and we hit it off well. He helped me change my visa so I could stay and start to work in his lab at the Massachusetts Mental Health Center.

TB: Could you say something about the Massachusetts Mental Health Center in the mid-1960s?

GG: The Massachusetts Mental Health Center in 1965 was a vibrant, very exciting place, but also a place in turmoil because on one side of the building were the wards where the psychiatrists were in charge and anything but psychotherapy was frowned upon, and on the other side of the building were the laboratories were exciting research took place. Some of the psychoanalysts on the clinical side were true believers. The research lab was run by Dick Shader and Al DiMascio and had young energetic psychiatrists like Carl Salzman and Roger Meyer. They did exciting work. I got involved in trials with benzodiazepines in symptomatic volunteers. I did a study comparing oxazepam and chlordiazopoxide

in symptomatic volunteers, studying the effect of the drugs on hostility and finding a paradoxical effect. Subjects given chlordiazepoxide showed increased hostility whereas subjects given oxazepam did not. Al DiMascio was my first mentor. He was incredibly energetic, bright, and likable. He was also a true believer in the future of psychopharmacology. In some ways he was very much ahead of his time. He had a computer already and was learning to analyze data because he knew that computers were going to be the thing in the future.

It didn't take me long to realize that without a valid medical degree in the USA, I had only limited options so I decided to take the plunge and started my residency at the Boston State Hospital where Milton Greenblatt had just initiated a number of pioneering community programs which started to empty the wards. It didn't take me long to realize that psychopharmacology was the future. Psychotherapy for schizophrenics didn't seem to do much. So, I thought I would need to learn more about psychopharmacology and using medications.

TB: So, you had your residency in psychiatry at the Boston Sate Hospital?

GG: I went to the Beth Israel Hospital in my third year for more traditional training. It was useful because at Beth Israel I got exposed to more verbal and educated patients than at Boston State. After Beth Israel I returned to Boston State and stayed for the next 8 years. My main reason for staying was the arrival of Jonathan Cole who took over as superintendent of the Hospital from Greenblatt, and created a very exciting atmosphere. He did the same there as he did on the national level as head of the Psychopharmacology Service Center of the NIMH; he attracted people with interesting ideas and helped everyone to do research, to get funding and he supervised them. He attracted a number of researchers and I worked with quite a few. Eventually there was a plan for a research institute to be built there.

TB: Could you say something about your research?

GG: I started under Jonathan Cole's mentorship and I did a number of studies with antipsychotics. I was interested in optimizing the use of psychotropic drugs and especially of antipsychotics. I did some studies to assess dose - effect relationships; I felt the dosage variable was not sufficiently appreciated, and found that in low doses some drugs had completely different effects from high doses. I noticed that small doses of neuroleptics could be used for conditions other than psychosis, such as anxiety and depression. I did a study on thiothixene and found that in low dose it had some antidepressant effect with improvement in mood and energy. We used scales like the BPRS for measuring changes, as well as outcomes like participation in rehab programs and found that

patients on low doses were more likely to participate. I studied new drugs developed for the treatment of anxiety. I did a pilot study with propranolol in high doses in schizophrenia and found that the substance was not safe to administer. I did an intriguing study on a medication called Thorastal, which was a combination of Thorazine (chlorpromazine) and Stelazine (trifluoperazine). This was a comparison study with the components of the combination and our findings did not even show a difference in sedation between the single drugs and the combination, which clinically did not make any sense. But findings in research studies do not always jive with what one sees in the clinic. Boston State in the 1970s was an exciting place, and some of our studies were directed at assessing how discharged patients fared. I did some work with family care patients and studied their social adjustment.

TB: Any other research projects you would like to talk about?

GG: We did a study way back at Boston State on clozapine. We had positive findings but we didn't see anything dramatic. .Jonathan Cole went over to McLean Hospital from Boston State in the late 1970s. I joined him, and stayed with him for years while I continued my work part-time at Boston State. Jonathan Cole, besides being an eminent researcher, was also a superb clinician. He had tremendous communication skills. In the late 1970s when the literature was somewhat dogmatic with respect to mono-therapy I saw Jonathan's patients walking out of his office with three or four prescriptions and they did well. The major research program I was involved in at McLean was our tardive dyskinesia (TD) study. It involved close to 200 patients who developed TD. We followed them for up to 15 years. This enabled us to get data on epidemiology, risks factors, course and treatments. To summarize our findings we came to the conclusion that tardive dyskinesia really was not as malignant as usually perceived. After five or ten years, patients managed well and got better rather than worse. The situation about TD changed radically with the arrival of the atypical antipsychotics in the mid 1990s, of which clozapine was the first and remains the gold standard.

TB: Would you like to comment on you experience with atypical antipsychotics?

GG: There are still major questions about the efficacy of atypicals. They don't seem to be as effective in the office as one would like to see. I combine them with more potent dopamine- D_2 blockers to get a better response.

TB: Could you tell us something about some of your other projects in TD?

GG: I had done a long term follow-up study with Daniel Casey in Hungary where TD seemed to be less prevalent than here. This was an interesting

study. I became impressed with the particular clinic where it was done because they used a great deal of drug combinations. They didn't seem to be more or less effective than mono-therapy. The clinical findings with antipsychotics were comparable in Hungary and the USA.

TB: When did you start your private practice?

GG: I started private practice on a part-time basis in the 1980s and I am still seeing many of my old patients. It is interesting to age with them. I have patients I have followed for 25 or 30 years.

TB: Is there anything else you would like to add about you research or research in psychopharmacology in general?

GG: I am in some ways a dinosaur by insisting on clinical science. In terms of my practice, I think the appearance of Prozac (fluoxetine) was a watershed. It made my practice with drugs almost 50% easier overnight. I had the wonderful feeling I could now give a medication to a patient and I didn't have to worry about getting called about side effects at night. Most of my patients for whom I prescribed the substance got better and liked to stay on the drug. Most patients today come with a drug history and that of course dictates the choice of drug to be used in treatment. Most psychiatric diseases are chronic and they are controlled but not cured with drugs.

TB: When were you elected a member of ACNP?

GG: In 1987. I am honored to be a member of ACNP and I look forward attending the Annual Meetings. I think this organization has done tremendous work for science and patients.

TB: Thank you, George.

GG: Thank you, Tom, very much.

BURTON J. GOLDSTEIN

Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December 13, 2001

TB: This will be an interview with Dr. Burton Goldstein* for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College in Hawaii. It is December 13, 2001. I am Thomas Ban. So, Burt, let us start from the beginning. Where were you born? Tell us something about your education and so on.

BG: First, let me say what a pleasure and honor it is to be here this afternoon to be part of this wonderful organization that has meant so much to me. I often get asked which is my most important organization and I say, "It's the one where I don't have a diploma hanging up, the American College of Neuropsychopharmacology." I was born in Baltimore, Maryland and educated in its public school system; elementary school, junior high school and high school. On graduation, in 1949, I entered college at the University of Maryland, School of Pharmacy. I had never thought about being a physician. I was interested in pharmacy. But during four years working for my Bachelor's Degree in Pharmacy, I became interested in pharmacology and pharmacology and chemistry were the courses I did best in. Upon graduation, it was during the Korean War; I was drafted and found myself in infantry basic training. It was quite a challenge. I learned that I had talents I never thought I had. They sent me to advanced infantry basic training and it was interesting because I got pushed to my limit and I learned what I could do. When my time was up I had to figure out what was I going to do with my life and I thought, maybe I'll go to medical school. That was a rather ambitious undertaking, because I did well in pharmacy school, but I certainly wasn't outstanding in terms of grades. I applied to the University of Maryland and figured, if I can't get into my home state university, I'm not going to get into any other. I got accepted on the provision that I take a year or two of liberal arts courses.

TB: What year was that?

BG: That was in 1956. I entered medical school in 1956 and graduated in 1960.

TB: So, you did not pursue a career as a pharmacist?

BG: I never did. The pharmacy helped me, financially, to get through school. There was the GI Bill and I was getting, I think, a hundred and eighty dollars a month but I had to pay tuition out of that and everything else.

---

* Burton J. Goldstein was born in Baltimore, Maryland in 1930.

As a pharmacist, I could work in the summers in the pharmacy and I made all of two dollars an hour, but I worked sixty or seventy hours a week and made a hundred and twenty or a hundred and thirty dollars. In 1956 that was a lot of money. So, I was able to pay for medical school. My GI Bill ran out, as I recall, at the end of my junior year but I got a scholarship for my last year of medical school. I graduated in 1960, and, like most of us, was trying to decide what path I should go. My role models were some of the people in the department of psychiatry; so I decided to go into psychiatry and went to Miami to do my internship, then applied to Jackson Memorial Hospital, a large community hospital of the University of Miami, for residency. I had an NIMH Fellowship during my residency years, so I took off in more of a research direction. But our program didn't encourage research, because we were a county hospital. At that time, south Florida, particularly Miami, was undergoing a lot of turmoil and transition because of Cuba. Castro had just come in the late fifties and early sixties. I was there in 1960 and 1961, as an intern and from 1961 through 1964 as a resident. At that time there were a tremendous number of well qualified Cubans there because of the persecution. That went on for several years and the population of Dade-county served by the hospital was exploding. So our clinical work overshadowed almost anything else. Everybody was so involved in patient care that research was put on the back burner. But I persisted and I was able to get involved during my second and third years with folks doing psychological research. I don't even remember what they were doing but I learned some research strategies, research methodology that helped me. In 1964, I finished my training and our Professor and Chairman, John Caldwell said, "You know, if you're interested in research, why don't you stay on"? I was flattered and honored. So, I was able to join the faculty and I remember him telling me, "Well, I'm going to be able to pay you ten thousand dollars a year. That will be your salary and for seeing patients, you'll get another ten thousand dollars". I had never heard of that much money in my life, so I thought I was going to be a very, very wealthy person, not just having an opportunity of to become involved in research. Then I met some of the people at the Psychopharmacology Service Center, which included you, your dear friend and colleague, Heinz Lehmann as well as Jon Cole and George Crane. By that time we had already done a couple of studies with haloperidol and when I started talking to George, he said, "You know, not too many people in the country have much experience with haloperidol, would you like to get involved in a study"? That was flattering, because I didn't know very much about federal grants or anything of that sort

and so George, as obsessive he was, and he really was obsessive, put a protocol together. It was a wonderful learning experience. It was a duplication, on a small scale, of the nine hospital collaborative study, the pivotal study in determining that neuroleptic drugs were effective in the treatment of schizophrenia which was completed in 1962.

TB: After completing your residency you stayed on the faculty of the Department of Psychiatry at the University of Miami. Didn't you have something published while still a resident?

BG: Right. I began publishing while I was still a resident. Our first paper was on Cogentin (benzotropine mesylate.) It addressed whether it should be used before EPS developed or after the first signs. It was a terrible paper and it was rejected by a couple of journals before, finally, it got accepted.

TB: So, your interest was in clinical pharmacology?

BG: It was something that caught my interest, even though I didn't know any people in the field, and I was fortunate to have opportunities to pursue it.

TB: How did you get involved with the Cogentin study?

BG: That came from watching patients develop EPS, who were on Trilafon (perphenazine) and Stelazine (trifluoperazine) They were taking high doses and developed extrapyramidal side effects. But what really triggered it, now that you ask me the question, was that when I was an intern, a man came into the emergency room and his jaws were locked. Everybody thought he had tetanus, but when I asked him to write out what medications he was taking, he had been on Trilafon or Stelazine. He was having a dystonic reaction. There are very few times in my life I've been called a hero, but the people in the emergency room thought I was really smart, especially when I gave the man one or two milligrams of Cogentin IV, and he could talk again. Gosh, I could walk on water that day! That may have been behind the Cogentin study.

TB: Could you say something about the study?

BG: I don't remember the results clearly but I think it was that you could not predict who was going to get EPS, so it probably wasn't worthwhile giving Cogentin prophylactically. I learned research methodology from the study, and that was the beginning.

TB: Did you do any other studies while a resident?

BG: No, at that time I was working with a psychologist doing research in some abstract field so that was the only pharmacological work I did as a resident. The University of Miami was only about ten years old and the Department of Psychiatry had only four full time psychiatrists. It was a very young department trying to take care of enormous numbers

of indigent patients; the clinical load overshadowed everything. That takes us up to about 1964 and meeting George Crane, who helped us to design the haloperidol study. I was fortunate that along the way I met Dean Clyde who had come to Miami a couple of years before, to set up the biometric lab at the University. The teaching hospital is in the center of the city and the University is on what's known as the Coral Gables campus, sixteen miles from where Dean's shop was set up. Dean was a unique individual. He was, in many ways, a loner, but Dean and I had a rapport that was wonderful. We had a close and not just professional relationship. What impressed me about Dean was not only his dedication but his abilities. He set up this biometric lab on the forth floor of a brand new building that was half of the size of a Costco warehouse with a whole floor for all of Dean Clyde's computers. That was just overwhelming and I got to work with him on the Cuban refugees. When the refugees were coming into Miami, they would come to what was known as Freedom Tower where they had all kinds of social service support. Dean was asked by the state department or someone to administer the Clyde Mood Scale to these people. One of the humorous events was, when Dean Clyde said, "You know, all these Cubans are coming and the scale is in English. We need to translate it". So, I got one of my faculty members, who had just come over from Cuba, to translate the scale. He was a very erudite physician, trained in Boston. He knew English and he knew Spanish and he translated the Clyde Mood Scale into Spanish, but none of the people coming over could understand his upper class Spanish. Then we found a person of lower social status but no one could understand him either. Finally, we were able to find a social worker who succeeded. When we started our haloperidol work with George Crane, Dean was part of setting up the design. I wish I had the slides from that study. It would be fun to look back now, thirty-five years later. We could keep patients in the hospital for three months. Today, we keep people in the hospital for four days. But then we had a design in which patients were treated with Haldol or Trilafon in a blinded design for eight weeks. At the end of eight weeks, we'd have a clinical conference and if they were considerably improved, we would watch them for another eight weeks. But if they relapsed, they would be started on the drug they improved on. But, at the end of eight weeks, if they didn't improve, they were crossed over to the other drug and treated for another eight or sixteen weeks. At the end of the study we found haloperidol was an effective neuroleptic drug, which sounds foolish today, just as the nine hospital study sounds foolish today, because everybody assumes we always knew those drugs were very effective.

The most interesting part of that study was that, at the end, we could firmly conclude that the dose of haloperidol should be fifteen to twenty milligrams a day. I remember that Dick Shader from Boston called me and asked, "Burt, what is the dose of haloperidol"? And, I said, "Dick, it's sixteen to twenty mg. a day, you don't have to go up to those mega-doses". What actually happened was sort of an industry push. They talked about rapid tranquilization, but rapid tranquilization really translated to rapid haldolization. So, a lot of Haldol was sold; people didn't need ninety milligrams of Haldol, twenty mgs was just as good.

TB: Today, you could go even lower.

BG: Sure. We were particularly honored because the introduction of haloperidol, once it was approved by the FDA, took place in Miami. We had a symposium and Paul Janssen was there. At the same time, we were starting several industry sponsored clinical studies. Then, I wrote with Dean Clyde, the chapter on the butyrophenones in ACNP's *Psychopharmacology, A review of Progress from 1957 to 1967*. We put John Caldwell's name in as a third author because he was always a tremendous support.

TB: So you did your research with haloperidol in collaboration with Dean Clyde?

BG: Yes. I think Dean was probably the person who got that study for us, because I was unknown and Dean was a known entity; he certainly deserves the credit.

TB: It seems that study was very important in your career?

BG: I was fortunate because I began to meet a lot of people. I met Nina Schooler, Jonathan Cole, Arnold Friedhoff, Ronnie Lippman and Jerry Levine to name a few. The two people I worked closest with were Leo Hollister and Bert Schiele. They were not only, professional but close personal friends. Yesterday, at the memorial services, my eyes welled up. I just thought about Leo and what a tremendous human being and wonderful man he was. I knew him so well in a very personal way along with his son, Matt, who was somewhat autistic and schizophrenic, and how Leo took care of that child. That young man would have never survived if it was not for Leo's nurturing; that was another side of him. I've been so blessed to be able to work with so many wonderful people.

TB: Let's get back to chronology. Are we now in the late 1960s?

BG: We are into 1967 and we were watching a lot of Karl Rickels' work because our hospital was similar to Karl's hospital, the Pennsylvania Hospital that had a large indigent population. We became aware, as did Karl Rickels, that there were influences to drug response and side effects that went beyond and outside the pharmacology of drugs. As an

example, if you had a lower socioeconomic group of people that were on welfare, and did not need to get to work in the morning, they didn't object to the sedative side effects of a drug, as much as a middle class person, who had to get up and go to work. To overcome this problem Karl Rickles was fortunate to get primary care physicians as part of his network. He had a cadre of both indigent and private practice patients, thus he could study the same drugs across these groups to have a better sense of what the efficacy and side effects might be in different populations. We tried hard to replicate what Karl did but we couldn't do it and ultimately came up with the idea to recruit symptomatic volunteers, a population similar in socioeconomic factors to private patients and the question was whether these subjects had similar levels of "psychopathology" as Karl's patients. We worked with Leo Hollister and John Overall evaluating three study groups; one, an indigent population, second, a private practice population, and third, a "symptomatic volunteer" population that we get recruited via public notice. We designed a study to evaluate the efficacy and side effect profiles in these three groups and also we obtained demographic and sociologic data so that we could not only determine response to treatment but also find out if the "Symptomatic volunteers" (SVs) were more similar in their response to the indigent or private practice patients.

TB: When was that?

BG: We began this work in 1968 with a grant to study the symptomatic volunteers and where they fell into the spectrum. And, as it turned out, our hypothesis was accurate that these subjects were socioeconomically similar to the private practice patient in their response to medication. Our group were the first to utilize this SV population for drug studies. This morning, I asked Paul Leber of the FDA, "Paul, how can I find out how many drug trials have been done since 1970, using recruited subjects"? And, he said, "I have no idea; you'd have to ask the drug companies". Obviously, they don't have any idea either, but I would imagine that, just not in our field of psychiatry, but also in other medical disciplines you can find many studies done with symptomatic volunteers, recruited by advertising in newspapers or TV. I am very proud of our work because the use of symptomatic volunteers has facilitated clinical drug development across the world. I doubt that there would be enough patients to conduct most medication clinical trials without the use of symptomatic volunteers. I believe this work has facilitated drug development and I feel very good about that.

TB: So, the idea of working with symptomatic volunteers comes from you?

BG: I published on it first in 1970. As I look back on my career, that's probably my greatest contribution because it certainly facilitated drug development and drug discovery.

TB: By that time you attended, quite regularly, the annual ECDU meetings, right? Besides the grant for the haloperidol study, you also had a grant from NIMH. Is there any other area of research you had been involved with?

BG: We were doing a lot of drug trials, but then we became aware of the flip side of psychopharmacology, substance abuse. There was a Catholic Priest in the Miami area, Monsignor Brian Walsh, who came to see Jim Sussex, the Chairman of our department and myself, telling us, "You know, we're having problems with our methadone clinics. Msg. Walsh felt that many of the Methadone patients were depressed and the methadone treatment alone was not helping their depression. He asked if we would look into this. I reviewed some of Freud's early literature on the use of Cocaine to treat "melancholia." We believed that one could make a pretty good case that many individuals that got hooked onto heroin, cocaine or other drugs were trying to treat themselves for depression. I remember talking to Mitch Balter about this at NIMH and we submitted a grant proposal to NIDA to study this question. Our thinking was that some of these individuals were not adequately treated, because nobody was treating their depression. So, we set up a Methadone Clinic, under the auspices of Monsignor Walsh. In the study when someone came into the methadone program, we assessed their depression on the Hamilton Scale and four or five weeks later, we would repeat it. Those patients whose Hamilton scores indicated moderate or severe depression were randomly assigned to one of two treatment groups; half the group was treated with methadone plus an antidepressant and the other group with methadone and placebo. Patients received medication daily in a 12 week double blind study. At the end of the study there were decreases in depression scores. However, the greatest change observed was in the patients' behavior. They seemed to get into less trouble with police. There was a great deal of improvement, mainly in the area of behavior, fewer arrests, improvement in relationships etc. If you follow the literature on heroin addicts and methadone programs, there is a body of literature which has been emerging over the years that these individuals may respond to antidepressants plus their medication, because of underlying depression. While we were doing this study there was a young man from Yale, looking to get involved in psychopharmacology. I was able to obtain a career teacher award from NIDA for him. He seemed to have a real interest in a teaching and research

career. The young man's name is Brian Weiss, and one day I asked him, "Brian, would you be interested in an academic career and he said, "Yes". Then we put a grant together with me as PI and Brian as a Career Teacher and we got the grant for three years. In the second year of the grant, Brian came to me and said, "You know, I don't think this is really what I want to do. I have an opportunity to go over to the Mt. Sinai Hospital where they are going to start a Department of Psychiatry". Mt. Sinai is a private hospital in Miami Beach, a very well funded hospital with about six hundred beds. It is very different from the Jackson Hospital, which cares primarily, for indigent patients. I said, "If that's what you want, I wish you the best of luck". So, Brian went to Mt. Sinai and begins to see a lot of private patients. The next thing I know, Brian is involved in past life therapy and writes a book," *Many Masters, Many Lives ,* and became very, very famous. Now, there's about a year waiting list for patients to see him and his charge is about five hundred dollars an hour to take you back into a life you may have had before. While it was a disappointment for us, it gave Brian Weiss stardom and recognition around the world; however, we lost our Career Teacher Award since Brian left in his second year of the program. I imagine this is not an unusual happening in academia

TB: It seems you moved from research with psychotropic drugs to addiction research?

BG: Not completely. Had I stayed more with psychopharmacology I probably would have more recognition in that area but I've always seen myself as a person whose allegiance was to the medical school, first, and to me, second.

TB: I see.

BG: In the late 1980's I received a call from the Department of Education and they said that they were establishing a national program across the United States. This was to be an educational program to reduce the demand side of substance abuse in elementary and junior high school students, and they would like Miami to submit a proposal along with five other regions in the country. It's hard to say, no, when you're asked to be part of a program with so many potential benefits for children. We submitted a proposal together with some other people, and that was funded for about six or eight years, up into the mid nineties. I was the PI for the portion of the study that came out of Miami which covered a large geographic area on the west to Tennessee, and the north to Virginia. I think the project did some good, but it's always hard to measure, because one political administration puts emphasis on supply and goes after the people that grow and bring drugs into the

country, whereas another puts emphasis on reducing demand. Working under an administration that was looking at reducing demand we did a good job. When the funding switched, to increase the number of DEA agents, helicopters and people that would do interdiction, we had to close shop.

TB: In addition to your research activities, you also served as Vice-Chairman of the department. For how many years were you Vice Chair?

BG: I had been Vice Chairman for ten or eleven years. From 1972 through 1983. Jim Sussex, who was Chairman, retired in 1983 and I was asked to be Interim Chairman. I was a serious candidate for the job of chairman but the Dean had a policy to fill all vacant Chairs with outside candidates in order to bring new ideas into the school. I was very disappointed for a few months. Then one of my friends said, "You're going to be the happiest faculty person in about three months". I didn't believe him, but he was absolutely right, because I could go on teaching, doing research, and not have to worry about taking care of everybody's salary and doing the things chairmen do.

TB: When did Carl Eisdorfer become chairman?

BG: Eisdorfer came in 1986.

TB: And you continued with your research. Now you did some research with tricyclic antidepressants, but that had to happen before.

BG: In the late 1960's and early 1970's we studied several tricyclics.

TB: You had already talked about some of your research with doxepin. Did you work with any of the other tricyclics?

BG: We worked with desipramine and protriptyline.

TB: Didn't you do also some work with nortriptyline?

BG: Yes and many others.

TB: Imipramine?

BG: We worked with most of the tricyclics and with trazadone. In the early 1980's we worked with the SSRIs. So, we've worked with a whole spectrum of antidepressant drugs. We also worked with many of the anxiolytics that never came to market.

TB: Are you still working with antidepressants?

BG: No. In 1995 the University expanded the Drug Testing Program for the Department of Athletics, and I was appointed as Medical Review Officer. The program has been recognized by the NCCA as a model for Drug Testing for intercollegiate athletic programs.

TB: Any other project you would like to talk about?

BG: I also work in the Health Service Research Center at our University with colleagues from different disciplines funded by NIDA and headed by Clyde McCoy PhD, an internationally renowned Epidemiologist and

Chairman of Epidemiology at our school. The concept of "Center" bridges traditional departmental lines and so you're able to work with colleagues in different disciplines, who may have similar interests. We have a large number of chronic drug users in the South Florida area and one of the problems has been how these individuals get into the health care system and how the health care system reacts to them. Our Center is focused on chronic drug users. In the first phase of our first project subjects complete the Zung Depression Scale. Thirty-five to forty percent fell into the moderate to severely depressed range. The question was, are these depressed chronic drug abusers different from non-depressed chronic drug abusers? Depressed chronic drug abusers differed from the non depressed group in several sociodemographic and clinical ways including more females than males. We also found that depressed drug users are less likely to be working, more likely to have multiple somatic complaints, and their point of entry in the health care system is generally the emergency room as opposed to a clinic or a primary care physician. Going to an emergency room is an expensive proposition and we figured out that on average, a depressed substance abuser costs the system somewhere between fifteen hundred and two thousand dollars more a year. The second phase of this project plans to stratify the subjects into three treatment groups, antidepressant medication, antidepressant medication plus psychosocial intervention, and a third general control group to see if treatment of depression might have a positive effect.

TB: Is this project your primary involvement these days?

BG: Yes, I'm not doing clinical trials now. As a senior citizen, I'm a mentor to those in the department who want to do clinical trials, helping them to develop their protocols and their research strategies. .

TB: When did you actually stop doing clinical trials yourself?

BG: In 1993 or 1994, for administrative reasons. Dr. Eisdorfer wanted to reduce the number of divisions in the department and wanted faculty to do clinical trials on their own and not as part of a division.

TB: But you were involved until that time. Were you involved with clozapine?

BG: My division did a lot of work with clozapine; we did a lot of work with atypical antipsychotics, but my personal interest has probably been much more with antidepressants than with antipsychotics.

TB: Didn't you do some research with mood stabilizers?

BG: This has been mostly done by Paul Goodnick, in the department.

TB: Of all of your contributions, which one, would you consider the most important?

BG: I think the work with symptomatic volunteers. I'm very, very proud of that. I think the other contributions have been more on a local level, for example starting a psychopharmacology program at the University of Miami. On a national level, my involvement has been with the ECDEU, the NCDEU and with ACNP. I've been on various committees of the college over the years. I tend to be low-key, someone that's part of the team, rather than the team leader.

TB: You mentioned at the beginning, you worked with Leo Hollister and Bert Schiele. What did you do with Bert?

BG: We worked very closely together in some of the early NCDEU collaborative studies. Leo and Bert were my mentors and role models. I hadn't worked with you as much but I remember being at a Montreal meeting, reporting on our work with the thioxanthenes, that you and Heinz Lehmann organized. I did a lot of the work, as you did, with Navane, and the thioxanthenes.

I guess the most humorous person I've ever worked with was Nathan Kline. Nate was funny and we had a wonderful relationship. I would get calls from Nathan, every now and then, at odd hours in the morning telling me that he was flying in the Pfizer airplane between LaGuardia and Groton and I'd say, "Well, Nathan, why are you calling to tell me this? Is something going on"? He said, "No, I just wanted you to know where I was". There were things of that sort. Once we were talking about setting up a teaching program for psychopharmacology for Haitians, because he was very much involved with the government of Haiti.

TB: He created a psychiatric research institute in Haiti.

BG: Unfortunately, he became ill and was never able to pursue it.

TB: During the years you have published quite extensively. Would you like to elaborate on any of your papers?

BG: Recently Paul Goodnick and I published a three part article on the SSRI's in the International Journal of Psychopharmacology that addressed the pharmacology, efficacy and adverse effects profile. That's the direction I'm moving in now, in terms of developing review papers and trying to look at the totality of the field, as opposed to a particular clinical trial or subject. We published on a group of chronic drug users last year in the Annals of Medical Sociology. That's where I am at this point in time.

TB: Are you still working in the department?

BG: I wear several hats in the department. I am involved in the supervision of residents. I am very involved in the Department's Division of Behavioral Managed Care. My plate is pretty full.

TB: When did you become a member of the ACNP?

BG: I became a member in 1967 and a .Fellow sometime in the seventies. Then, I became a Life Fellow about five or six years ago.
TB: Which committees did you serve on?
BG: On the Finance Committee. I've also been involved with the Liaison committee between industry, academia and the college. I try to stay active. I follow also the CINP.
TB: You were also active in the ECDEU program. Weren't you instrumental in moving the meetings to Florida?
BG: The problem was we couldn't get them out of Miami. Everybody was saying we want to go somewhere else but the powers at NIMH seemed to like Key Biscayne. So, I was certainly involved with the ECDEU.
TB: Were you involved in organizing those meetings?
BG: I was very much involved in the organization of the meetings.
TB: For how many years were you involved?
BG: I think for at least for ten or twelve years. I guess that's part of my personality. I tend to forget a lot of things that have to do with me, myself.
TB: Would you like to mention a few people you worked with at the university?
BG: I worked with Ben Brauzer. Ben was my earliest colleague and he had a real affinity for psychopharmacology. But, unfortunately, he had some heart problems and had to retire about six or seven years ago. And Hy Denber called me one day and he said, "Burt, I have this wonderful, wonderful resident, Roberto Dominges, whose family is in Miami, and he would like to come". He was one of the best recruits I've ever had. Roberto is a really solid citizen and a great clinician, unfortunately, his career in psychopharmacology lasted about ten years and, then, Carl Eisdorfer tapped him to take care of all the administrative research issues in the department. So he's not doing research but more involved in the protection of human subjects, issues that come up in every medical school, now. Richard Steinbook has done a great deal of good work in the area of atypical antipsychotic drugs. One of my most important contributions has been in mentoring people, even though some didn't stay in psychopharmacology they developed an appreciation of what clinical trials were about, understanding pharmacology and medications better. There have been a whole slew of them. Over the course of the years, we've had at least twenty-five or thirty people.
TB: You are professor of psychiatry and pharmacology at the university?
BG: And epidemiology.
TB: So you had appointments in three departments. Were you actively participating in the activities of the Department of Pharmacology?

BG: Only in terms of Psychopharmacology. I'm much more active with the Epidemiology people now than with the Pharmacology people, because of their Health Services Research Center, which is going to be a model program in terms of developing Centers for medical schools where colleagues can work together without departmental lines.
TB: Have you written or edited any books?
BG: Way back in the past I was involved in editing four.
TB: You were involved in organizing several symposia?
BG: Yes, a haloperidol symposium and a thiothixene symposium. I had a lion's share of responsibility in organizing the haloperidol symposium
TB: Are you the recipient of any honors or awards?
BG: I am listed in Who's Who in America, Who's Who in the World, and Who's Who in American Medicine. In 1994, Good Housekeeping had a listing, and I was listed among the 183 Best Mental Health Professionals in the Country and among the 22 Best Known Physicians treating depression. I was the recipient also of some teaching awards at the university.
TB: Is there anything else, you would like to mention?
BG: I'm very proud of my family, my wife Linda, has always been a wonderful inspiration and my soul mate. We have six great kids, the Brady Bunch, and they're all wonderful. They're not so much kids. They go from their thirties down to their twenties, but they're all very good kids. They've all made us proud. Unfortunately, none have gone into medicine, but we've been blessed in having a good family.
TB: So, with this, we should conclude this interview with Dr. Burt Goldstein. Thank you very much Burt for sharing this information with us.
BG: Tom, thank you so much.

GERARD E. HOGARTY

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 16, 2004

AT: I'm at the 2004 ACNP Annual Meeting in Puerto Rico and, today, it is my pleasure to be able to interview Gerard Hogarty.*

GH: Jerry is what I'm usually tagged with.

AT: You have an unusual route to ACNP. Why don't we start by finding out a bit more about your background, how you got interested in philosophy and social work and, eventually, psychiatric epidemiology?

GH: Well, quite by accident, I got out of graduate school in 1960, and at the time, the only references I knew of to clinical psychopharmacology were tranquilizers. That's how everybody referred to them in those days. After I got out of school I was working in a Public Welfare Agency in the District of Columbia and I ran into an old professor, who said the National Institute of Mental Health (NIMH) was doing a nine-hospital study on these new tranquilizers and one of the hospitals was in trouble. They needed a social worker to collect the history data and background, and this was unprecedented because nobody had ever hired a social worker in that role. So, I went to the Springfield State Hospital and talked with the investigator there, an old fellow, Martin Gross, who was to become my first boss. We had a very lively exchange, which I don't think I'm going to put on record. Suffice to say, he thought social workers had "soft heads and big hearts", and that my demand for seven thousand dollars a year was outrageous. But, we became the best of friends. He was like a second father to me. He started off saying that I didn't know much about mental illness. So, he stuck me as an admissions officer in the state hospital for about a year. In that hospital we admitted about 10,000 patients a year and we had 3,000 beds. I learned about schizophrenia from Martin and his colleague, Arthur Mandel. Both of these gentlemen had fled Europe prior to the Nazi take over. Arthur had been at the Vienna Clinic, and had worked with Sakel who introduced insulin coma therapy, and Martin had been a disciple of Emil Kraepelin. So, this was quite an experience. I only came to appreciate its richness with the passage of time. If I had an hour with a patient, I had at least an hour with one of those gentlemen afterwards, to go through the experience. It was terrific. It took me many years before I could get into the DSM system or the classification of symptoms. I thought like a European. I had to think of cases and try to draw up the thread through that. To this

* Gerard Hogarty was born in Boston, Massachusetts in 1935. Hogarty died in 2006.

day, I'm adamant the diagnostic systems we have are really classification systems. You need profound knowledge from the narrative of life to understand a person. Diagnosis is, understanding.

AT: Can we backup a little? I'm writing a book on the history of the minor tranquilizers and what you said is fascinating. You said psychopharmacology was understood by people, outside of neuroscience, as being tranquilizers. I wanted to know what involvement social workers might have had with tranquilizers.

GH: That's really at the heart of this. I was only a kid at this point. When I was at the Springfield State Hospital, they were at the beginning of studies on antipsychotics, trying to pin down their prophylactic efficacy. Their therapeutic efficacy was fairly well established in multi-site collaborative studies sponsored by NIMH. But the issue that remained was whether these drugs could act like insulin for a diabetic. Did they have a prophylactic effect? My training, in social work, had been mainly psychoanalytic. My colleagues and I were all of the opinion that medications were "symptom covers" and that "love" would be enough, so if you could provide the right kind of psychosocial treatment you wouldn't need to have medications with all their side effects. When I was in training, I remember getting patients from a local VA and the goal of treatment was to wean them off their "oral dependency" on medication. The experience at Springfield was remarkable. I'd seen more change in twenty-four or forty-eight hours in these patients than I'd ever seen in people who had years of psychotherapy. But that needs to be qualified; my career has been in developing psychosocial treatments to use in combination with medications.

AT: Was your work focusing on tranquilizers at Springfield Hospital, like Valium (diazepam) and Librium (chlordiazepoxide)?

GH: No, those are the minor tranquilizers. We were dealing with schizophrenic patients and the medication we used in the study was Thorazine (chlorpromazine) and drugs like Thorazine.

AT: That was the drug used in the study you were recruiting patients for?

GH: Yes. I was a social worker for that program but the whole operation, the major study out of Washington, was run by Jonathan Cole.

AT: The godfather of…

GH: The godfather of American psychopharmacology. Jon decided to do a second study using high doses of those drugs. There were hundreds of thousands of people in State hospitals with the diagnosis of schizophrenia and the hypothesis was they were under-medicated. As it turns out, a lot of them were over-medicated. But the hypothesis was they were under-medicated so they put together a seven-hospital study.

The coordinator was Bob Prien, a psychologist, and Jonathan asked if I would coordinate the social workers at the seven hospitals. I had a chance to travel with Bob Prien to seven hospitals almost every month in the eastern United States and it was quite an experience. We were like the odd couple. It was the funniest time in my life but I also learned a lot. Then the folks at NIMH figured out I was writing grants for Arthur & Martin, so Jon asked me to come to the NIMH. I went for a year and had a phenomenal experience.

AT: What year was that?

GH: 1966. I had this wonderful opportunity to work with people in the Psychopharmacology Service Center (PSC.). Nina Schooler and Sol Goldberg were there and I worked with Marty Katz, Ronny Lipman, Mitch Balter, Al Raskin, Jonathan Cole, and Helvi Boothe. These were wonderful people and, I learned methodology while doing my job. We had these people who put together the assessment instruments we still use today, and I learned about study design and analysis of experiments. At the time I was raising a family, still struggling financially, and the company I worked for back in Maryland said if you come back we'll double what you earn to write grants for us. So, I said sure, when do you want me to start"? What I had in my mind was doing a placebo controlled study, comparing medication with a psychosocial intervention, alone and in combination. This was the first study of its kind. Although there had been a number of medication studies, there was none that went more than six or twelve weeks and none had ever combined medication with psychosocial treatment.

AT: Why?

GH: Nobody paid any attention to psychosocial treatment because, first of all, there wasn't any good psychosocial treatment except psychoanalytic psychotherapy. So, I put together something I called major role therapy. People picked up on it; it became what is now called clinical case management. It was atheoretical and did nice things for people who were having problems. It was a mental health services approach, but had no relationship to the pathophysiology of any of the disorders we were treating. People thought that was pretty wild. For the description of treatments today we need a big manual, but then the description was about a paragraph. I remember hearing, "Who is this social worker asking for a multi-site outpatient study"? I had a two-day site visit with about eight people. Well, I got that grant and we did the first long term placebo controlled maintenance study. We had almost four hundred patients; I think it's the largest controlled maintenance study ever done on schizophrenia.

AT: Where was it published?

GH: In the Archives of General Psychiatry in the early seventies. The project started in 1967 or 1968. It was awesome. Of course, patients were dropping like flies on placebo. We had almost two hundred patients on placebo and almost two hundred on medication, and then randomly assigned patients to major role therapy or not. And a couple of big things happened. We absolutely pinned down the prophylactic efficacy of antipsychotic drugs. About forty percent of patients on medication had a relapse in that two-year period, whereas eighty percent or more relapsed on placebo. A number of our patients made the Baltimore newspapers by acting out in the community. We were counting the times we made the newspapers. I was so upset. Right now, if you had a study like that, you'd have to call it off midstream. As a matter of fact, it would be very hard to get placebo studies approved today and even harder for maintenance treatment.

AT: By calling it off, you mean putting the patients back on the medication?

GH: Sure. I remember Nina Schooler saying, "You know, no one's going to do this again. You've really got to nail it to the wall". Outside this small group of biological psychiatrists, nobody at the time really believed in medication. Even today it can be an issue. I wrote a book a couple of years ago on one of our recent treatments, and in the review of the literature, there were still textbooks decrying the need for medications, and this was in 2002. So that belief has died slowly. In the 1970's, I was without a professional identity. Other social workers didn't want to touch me with a ten-foot pole. I had converted and joined the enemy, the "agents of mind control". But I had good friends from other disciplines so I carried on. We pinned that down and we also began, for the first time, to get a sense that the combination of medication and psychosocial treatment took you further than you would ever get with medication alone. That was a big observation. The most astounding thing to me in that study was that psychosocial interventions could have a profound negative effect under certain circumstances. If a patient received the psychosocial intervention and the placebo, his adjustment was far worse than those patients who received the psychosocial intervention with active medication. In fact, those people on placebo alone, who survived without a relapse, did better than people who had the psychosocial intervention and placebo. That occurred at all three clinics. It was reported first by family members, at about eighteen months. By two years, physicians and social workers all reported this profound interactive effect. You can never test for an interaction unless you have placebo controls. So, all of our future studies were

simply add-ons; everybody was on medication but some received the psychosocial treatments and some didn't. But this study was a classic two by two study design, with a control for medication and for psychosocial treatment. After that study people began to look at me, and say, "You know, he's a very interesting fellow. He's not opposed to medications, and he's got something else to add". So, that was the beginning. But a lot of critics said, "Patients often don't take their medication, but if it was guaranteed medication was taken they would have got much bigger effects for medication alone, and the combination of medication and psychological treatment wouldn't have mattered". So, I repeated the study with a smaller sample. It was in the Nixon years and there wasn't much money to do psychosocial treatment trials in schizophrenia. So, we did a study where patients either received an active injection of fluphenazine decanoate or a sesame oil vehicle, which was essentially a placebo. If you got the sesame oil vehicle, you also took an active oral medication, fluphenazine hydrochloride by mouth, and if you got the injectable fluphenazine, you took a placebo pill by mouth. So, everybody got a pill and an injection. The belief was, if medication was guaranteed, then relapse rates should be much lower in patients in the injectable fluphenazine group than in the patients that were getting oral medication. Was that correct?

AT: Yes.

GH: Wrong. It didn't matter. We had the same relapse rate at the end of a year on oral medication as we had by injection. It was only over time we could see the advantage of depot medication. That was a shocker. I held onto the results of that study for about a year or two. My colleague, Nina Schooler, was doing another collaborative study through NIMH on oral versus depot fluphenazine and came up with the same finding. So, I said, "I'm going to publish it". If I had published when we first had those results, I would have been laughed out of the field, because, people would have said, "That's what happens if you have social workers doing psychopharmacology trials". So, we sat on that one for awhile. That observation certainly revolutionized my life and did so for my colleagues around the world, in the field of psychosocial treatment. It was transforming, because the message was that even when you guarantee the receipt of medication by injection you still have this high relapse rate. Why? A drug is a drug. Why were these people relapsing? So that made us to begin to look closely at the environment. What is it in the life experiences of patients and in the pathophysiology of these disorders that will drive the illness in a positive or a negative direction? At this point, it was the 1970s and I moved to Pittsburgh. I have

been in Pittsburgh for over thirty years now where I had the good fortune to hook up with Carol Anderson, a traditional family therapist. We were talking in the cafeteria and she was saying the approach to family therapy for patients with schizophrenia was chaotic. Everybody would leave a session, screaming or in tears, and the therapist would think that was a great session. One of the things that was going on at the time, were studies in England on "Expressed Emotion." The patients, who returned to households that were high in criticism, in expressions of hostility and in withholding warmth and regard, had a high rate of relapse. Learning about these findings I thought they were vulnerability markers that could be exploited for therapeutic purposes. So, we put together the first theoretically based psychosocial intervention for these patients. It was, in retrospect, very simple. If you could "cool" the environment and limit the demands placed on patients, in combination with medication, you would lower the relapse rate. So, we came up with something we termed "family psychoeducation", which has now spread across the field. We started our study in 1977, coined the term and published on it, the first time, in 1980. Now, there's psychoeducation for everything. The results were profound. We had zero relapse in the combination of family psychoeducation, medication and Social Skills Training. Social Skills Training was an indirect way we thought would lower the expressed emotion of a household. We'd analyze these videotapes, looking for the kinds of behaviors in patients that "drove family members up the wall". Then we would work on those behaviors with the idea that if we can modify them we would lower the "Expressed Emotions" in the family. The other approach, the family psychoeducation approach was a direct way to lower the emotional climate of the household. In our study, if someone received the combination of those two psychosocial treatments, no one had a relapse in the first year. I never saw a study before that had zero relapse. Nineteen percent of the people who received Social Skills Training alone or family treatment alone relapsed, and patients who were on medication alone had the traditional forty percent relapse rate.

AT: How did you do that? How did you get to go in and talk to the families, and teach them to guarantee compliance with your model?

GH: This was a revolutionary idea at the time. It was the first grant I ever had that I almost gave back. In the seventies, the prevailing belief system in the mental health field was that families caused this illness, so, they didn't really need education, they needed therapy. And, the major treatment available to these patients, outside of medication, was what I call, "familyectomies". You could remove the patients from their families and

put them in foster care homes or something like that. The tragedy was that, when you took the family out of the picture, patients were largely left without resources, because public systems were never there lifelong. It was terrible. We ran into the process of de-institutionalization and we weren't prepared. I know you're too young to remember seeing people on the streets. It was terrible.

AT: I've heard a lot about it. They were involved in the "revolving door syndrome", in and out of hospitals.

GH: Right. It was terrible. So families were ecstatic with our family psychoeducation approach. They loved to be involved and to have clinicians and mental health professionals around who would actually listen to them. We marketed family psychoeducation as a "survival guide"; what you need to take care of yourself and survive this horrible illness. What families did, intuitively on their own, might have looked sensible but in practice it could cause more trouble than not. So, a lot of what we taught them was counter-intuitive. But, at the end of two years, in that study, we lost the social skills effect, and so I got off social skills. It alienated a lot of my colleagues in the behavioral field that the effects went away. To this day, I'm not convinced there is great generalization from Social Skills Training. But family psychoeducation was remarkable. There have been about fifty studies worldwide on family psychoeducation. Thirty of them, I would say, were good studies, well-designed and conducted. They almost unanimously replicated our results. I've never seen anything like it. That's why we ask the question, how many patients in the United States have been exposed to family psychoeducation, as it was designed? It would have to be less than one percent, even today. The downside of my career has been that with increasingly effective interventions, we have seen less and less implementation. Now, you've got to remember that in the family studies, everybody is on medication, everybody. It's an add-on design I spoke of before where we added family psychoeducation and social skills combined with medication. We did an uncontrolled follow up, and found that once the psychosocial treatment was removed, it was much like medication alone. If someone stopped their medication, they would have a decompensation. John Rush is a member here, and I remember him saying, "Well, I guess, Jerry, there's no such thing as a verbal decanoate". There were expectations that if you had a psychological treatment, somehow it should last forever. First generation, conventional antipsychotics, were one of the big constraints working against psychosocial treatment. Most of the patients had extrapyramidal symptoms from because we believe they were used in too high doses. Invariably, if you had side effects, you had

to take an antiparkinson drug, and these drugs have high anticholinergic properties. People said "why should this matter to someone, who is in psychosocial treatment?" Well, if you are taking anticholinergics they affect short-term verbal memory, and every one of the treatments I designed, was based on someone's learning ability. So, we were operating against ourselves. One of the things I ended up doing during a period in my life was toxicity studies on these antipsychotic drugs. We developed a series of studies on what we called, the MED, the minimal effective dose, and found in a double-blind study that relapse rates with fluphenazine enanthate in high and low doses were not different. I got into trouble with our administrators because the first patient that relapsed was on low dose and they said "you know, we can't let you do this. We patch these people up on the inpatient unit and when they go to your program you lower the dose and they get sick again". I said, "Give me some time". So, the next person who relapsed turned out to be on the high dose. Then, the next one was on low dose, and so we got through it that way. Then, with a colleague, Joe McEvoy, we did an inpatient neuroleptic threshold dose study, with haloperidol, using the dose on which patients got minimal hyperkinetic rigidity, and that was around one to two milligrams a day. It was the conclusion of that study, that you're going to get as well as you're capable of ever getting with these meds on one or two milligrams a day and higher doses don't get you better faster or "more-better" They just give you more side effects.

AT: My limited understanding of how we encourage schizophrenics to continue taking their medications is having meds which don't affect their thinking.

GH: That's why I think compliance with atypical antipsychotics is much better than we ever had with conventional neuroleptics. That's a whole science I haven't gotten into. There's a psychiatrist here, Peter Weiden who is probably doing the most consistent work in that area. What I've learned about compliance is that you have to get into the belief system of the patient to understand it. As a matter of fact, we don't use the word, compliance, we talk about adherence. We want to understand how patients view their illness. When I came into this field, they said that eighty percent of people with schizophrenia had no insight about their illness. I don't believe that. The overwhelming majority of patients with schizophrenia in this country, at least, get "supportive psychotherapy," what I call, "warm medication". After the family psychoeducation study, we thought we needed to do something that would stick with patients longer and put them in better control of how to manage their symptoms. We did a psychological autopsy of relapse; the process that led

to relapse. Surprisingly, most of what was going on was affect dysregulation. Before you see emergence of problems in cognition, with disorganized thinking, hallucinations or problems of perception, invariably you find early affective cues. They'd get excited, depressed, anxious or withdrawn, that kind of stuff. So, we put together what has become an evidence based individual psychotherapy for schizophrenia. That took a lot of years. I didn't call it psychotherapy at the time, because psychotherapy had such a bad reputation that nobody would have funded it. So, we called it Personal Therapy, PT. It consists of strategies geared towards the patient's clinical state. We don't want to overwhelm the patients as we learned that precipitated relapse. We have three different stages of recovery and we had practice principles and adaptive strategies tailored to where the patient was. This approach was like a smorgasbord. You could pick and choose, depending on what the individual patient's needs were. We tried to get people to become tuned to their earliest signs of distress and, when they recognized those, we would provide an adaptive strategy. This was somewhere between skills training and a more developmental approach. I have gone full circle and now I'm into a developmental approach. Those studies on Personal Therapy were published in 1997 and we had a book out on that in 2002. But, lo and behold, things were better but not well. So, how did we find that out? I was talking one day with a good friend, a rehabilitation officer. He ran the local district in Pittsburgh for a long time in a nearby county, and he said, "You know, Jerry, we take your patients and get them jobs and back on their feet. But then they failed coffee break." In other words, there were rate limiting factors to a full recovery in informal types of socialization, initiating and trying to maintain a conversation, where patients had problems.

AT: How did you tackle this issue?

GH: One night I was sitting in the library and going through Spreen and Strauss' Compendium of Neuropsychological Tests and while reading test results of neuropsychological tests, like the Wechsler Memory Test, the Wisconsin, Measures of Cerebral Activation, I thought these must be norms for adult schizophrenia patients. Do you know what they were? They were the norms for normal pre-adolescents. I almost flipped. That's where our patients are from a neuropsychological development point of view. So, I thought, "I wonder what their social cognitive development is". I didn't know anything about that, but I was fortunate to have a good colleague who did. He said, "You better read Bob Selman's book," "*Making a Friend in Youth*". There it was, these normal pre-adolescent kids were also very egocentric, had difficulty seeing the

perspective of another person, and could never pick up the cues of social context, the informal rules of conduct that govern every relationship. For example, I have rules even when I'm sitting here, we have a camera over there and I have codes of behavior I have to follow, right?

AT: Right.

GH: So, we spent a lot of time thinking about why our patients fail. They fail, not necessarily because of their neurocognitive deficits. Those may be necessary, but they're far from sufficient. A lot of people are walking around with neurocognitive deficits. A lot of so-called, normal people come into our lab and they can't do these tests either, but they lead very wise and useful lives. They have a high social and emotional intelligence, even though their neurocognition may be bad and even their I.Q.'s might be a little low. So, we thought that the rate limiting factors that kept our patients from a fuller and more enduring life were due to problems in social cognitive development. I know the hot thing here today at this ACNP meeting is looking for new molecules and new receptors, and how to come up with a new drug that would help. But we did a study on what we call Cognitive Enhancement Therapy, CET, a small group approach. We piloted CET in the early to mid 1990's. We started a big study on CET in 1995 that ended in 2001. It took a long, long time to get it published. It just came out a couple of months ago.

AT: Congratulations!

GH: I had to beat back a lot of people, the behaviorists, the neuropsychologists, nobody liked it. But, this stuff is terrific and, now, it endures. We did a one-year follow up and the effects are still there. As a matter of fact, they grow. I've never seen that in schizophrenia. I've never seen effects of a treatment grow with time.

AT: What was next?

GH: I tried to put out a new initiative on a problem that no one had done well with in psychosocial treatment and the committee, in its' wisdom, said they weren't giving me any more money until someone replicated our findings with CET. I could understand that but I didn't agree. I believe science is discovery. I think replications of science are political decisions and I don't have any control over that, but at any rate I thought it was a good time to wrap it up. But, then I had the good fortune to connect with a colleague interested in replicating our finding with CET in first episode patients, with the idea they'd be younger and would have more plasticity reserve. It's been a tough study to recruit for; however, we're about half way through. The first cohort of people going through CET were getting some very, very promising results on increases in frontal cortex density, where there's probably increased

synaptic connectivity. Increased synaptic connectivity has been known to occur in animal studies but I don't think anybody's looked at that in humans, in patients going through treatment. With this early course study, we have been using a new instrument that was developed in the last few years, called the MSCTEI, the "Mayer, Salovey, Caruso Test of Emotional Intelligence". Our first twenty-five patients are through that randomized study. On the MSCTEI the controls are a straight line between baseline and one year, and the CET patients have tacked on twelve EQ points. They went from eighty to ninety-two in a year in emotional intelligence, so they're very close to the norm. That's very encouraging. I've almost finished the manual for CET. As I said before, it's been remarkable to me, that with every psychosocial treatment with increased efficacy that comes closer to the presumed pathophysiology of these disorders, the interest in the field to implement the new treatment has gone down. This is a paradox I don't understand. I've been trying to get opinions from my colleagues. One of my beliefs, rightly or wrongly, is that the curve of decreasing interest could be superimposed on a curve of increasing control by managed care organizations.

AT: I was going to ask you about that.

GH: The more managed care has taken over, the less likely clinicians or providers are to be able to implement evidence-based treatments. You've got this group of people talking about evidence-based treatment but the reality is there is less and less of it.

AT: And, evidence based psychosocial treatment especially, because it's labor intensive.

GH: It's expensive. But we figured out this Cognitive Enhancement approach, could be done reasonably. If you did it by the book, the way we did it, it would probably cost $1,800.00 per patient a year; it's a small group approach. In the community they're doing it at a cost of $1,300.00. Now, that's not a lot of money, and, even with Medicaid, which is the primary insurer for many patients, you can bill eighteen bucks an hour, or at least you can in Pennsylvania. If you had six or eight patients in a group, you could more than make your cost. So, I don't think it's the cost but I don't know what it is. It may be residual therapeutic nihilism that continues to characterize some people's thinking about schizophrenia. And the focus in the field to target different molecules that would enhance cognition. The theory is very good, and in time people will have more effective medications to enhance different aspects of cognition. But, right now the effect size of this treatment is a magnitude of about 0.1 to 0.39 and an effect size of .5 would be clinically very relevant. The guy on the street would notice that a person is different if

they change that much. The effect size of medications ranges from 0.1 to 0.4, somewhere around there. A year after the treatment ended we tested these patients again and the effect was still there. I've never seen an effect like that in any treatment. So, we have some evidence that the effects of CET last and, with the follow up study, we learned that they grew. There's a lag between neurocognitive changes and social cognitive, social adjustment and performance abilities but they catch up, which makes sense. If you improve a person's basic core cognitive processing it would take some time for them to use that. One remarkable thing is that CET is a group approach. In the original study, we had very chronic patients, people who had been ill for an average of sixteen years. After the study ended, forty percent of the CET patients went out and found another group to participate in.

AT: That is interesting.

GH: That was remarkable to me too. The current theory about withdrawal is that it's positive in that patients stay away from other people. I don't think that's true. They're very uncomfortable and they don't know the language or the rules. They don't know what it takes to form and maintain a relationship; that's an illness residual and something that can be taught. These patients can learn and they show us, day after day, that they can do it. It's remarkable; I only wish someone would use it.

AT: You're so enthusiastic about it!

GH: So, that's where we are. It's been a privilege to spend my life doing this. Whenever I look over my shoulder, I think I wandered into this field, completely unprepared with an antagonistic background in training that I had to overcome. These treatments wouldn't have been possible without medication, so that's why I've stayed close to ACNP. I've always had a soft spot in my heart for the organization. It's been a privilege and it's been fun, for the most part.

AT: I have a couple of follow up questions, in looking at the larger picture and one very selfish question. You talked about how groups like ACNP have accommodated your approach. To what extent has social work, in the same time period, accommodated the importance of drugs and some of the things that psychopharmacology offers?

GH: It's been a very, very slow process. You used to get a lot of people who were outspokenly antagonistic towards biological psychiatry and medications. That has become an indefensible position in the field of social work. Gratefully, there are a lot of young people, who are much better trained, really bright young men and women who have adopted a biopsychosocial approach. That's positive. Unfortunately, the people closest to the patients, in terms of providing services, have adopted

this recovery model. They don't want to hear the language of medicine; they don't like the theory of adjustment, they decry teaching patients to acknowledge their disabilities and try to adapt to them. My feeling is these disabilities are real and patients know they're real. We don't demean anybody's strengths in fact we build on them. You can't begin to teach compensation unless you know what you're compensating for. That part of this field tends to be dominated, unfortunately, by social workers who decry controlled trials, because they don't reflect the "real world", and say you've got to do effectiveness studies, approaches grounded on understanding people. That, to me, is an exercise in fishing without a net. It's morphed from a distinct anti-psychiatry and anti-medical model into an anti-biological psychiatry approach with some accommodation for the strengths model. I recently pointed out to some colleagues that the strengths model comes from nineteenth century American Protestantism. At the time, in the state hospitals, in the mid nineteenth century they were practicing moral treatment. Many of the superintendents of those hospitals were ordained ministers who look for the strengths of the person. Taubes wrote on this some years ago, and during my five years working in a state hospital, I observed it myself. For example, you'd go into a religious service, and see patients who were actively psychotic but acted appropriately during the service. So people would say, "See, with the right motivation, you can get anybody's strengths out." Or, you would see patients with a musical skill that was intact so they could play the piano or banjo even when they were actively psychotic. It is like a version of Phrenology, that there are areas of the brain that have distinct abilities and, even though someone has mental illness, these abilities are preserved and with the right motivation, which is always religious, one could see those strengths reveal themselves. It's the same movement that won't call patients, "patients", they call them consumers. It went from clients to consumers.

AT: I know.

GH: It's kind of a movement that thinks disability is stigmatizing. What we've seen from people who follow that model is they want to do what the patient wants. The patient wants a job so they'll get the patient a job. If the patient wants to go back to school, then they get them back to school. But, they may send someone back to school with a workload of five courses and the patient is back in the hospital within a month. When we work with patients who want to go back to school, we look at the person's disabilities, their processing difficulties, their working memory problems and lay out a course of study to do it in steps. We're going to get to the same place as the strengths people. It's just going to

take us a little longer. The goal is the same, but the way we go about it is very, very different. If a patient doesn't come to some understanding and adjustment to their disabilities they're going to keep repeating the past. Indeed, they have distinct disabilities, but they are not necessarily disabilities you can see. It's not like physical rehabilitation and physical medicine. The disabilities we have here are mental stamina, concentration, working memory, perspective taking, context appraisal, and so on. All these are problems and they can be remedied. So, that's where the field is. The hottest movement in public mental health is this recovery model and I'm on the outside of that.

AT: Some people would say schizophrenia is a really serious illness that if left untreated can cause a whole variety of grave problems. There was an editorial in the New York Times, a couple of days ago, by Carl Elliott and he was saying that the problem in American society is not the medications for seriously ill people but that we're all being medicated. It's like we have this desire to be evermore perfect, so we've embraced lifestyle drugs. We want to reengineer sexuality; we want to give ourselves no wrinkles, so we line up to get Botox; we want to have better sex we choose between Viagra and Cialis and if our kids aren't doing well in school, we put them on Ritalin. How do we respond to that and is there some merit to that?

GH: My belief is that it's important to distinguish whether a problem reaches syndrome proportion. Is it really disabling to somebody in their interpersonal relationships and their work performance, their personal comfort level, such that they can meet criteria and they've got a bona fide diagnosis? The analogy would be, people who have a clinical depression versus those who have blues every so often. What we see a lot of is intolerance for any disruption in mood, an intolerance of any disruption in relationships. Going back to social cognition, the highest level of social cognitive development is an ability to come to a realization that the other person is going to be just as unpredictable as you are, and, once you understand that, and come to terms with it, your life changes. The big success that people have, in psychological treatments alone for depression, are with people who don't meet the syndrome or clinical disease state criteria. In schizophrenia, I've not had to deal with that because being a little bit schizophrenic is like being a little bit pregnant; it's not a matter of degree, whereas, with mood disorders, they're all matters of degree. So, it's an issue of where are you going to draw that line? Clearly, the majority of people, who don't meet clinical criteria for depression, but are unhappy in their lives, with a spouse, with their sexual performance or their work, these people can do very well with

non-drug interventions seeking a better quality in life. The answer that I have is the answer the late Gerry Klerman, MD used to say, "the market place will determine its' value". These are marketplace decisions and if the insurance companies or people pay out of pocket and think it's helpful, they'll continue to do so. Another old friend of mine, Marty Katz, used to say, what the world needed was a cheap safe intoxicant, a five cent fix that was safe. I'm not much of a historian, but cultures have always been looking for ways to enhance life experience. One of the problems with schizophrenia is there's only so many public health dollars and we don't do a good job in this country with our chronic severely mentally ill, except when it comes to medications. Most formularies cover all these drugs and they're very expensive. I'm not saying they shouldn't be prescribed and that we should go back to the old drugs, because they're cheaper. But there isn't much money left over for anything else. That's what insurance companies and managed care organizations are looking at, the difference between nine-thousand dollars a year for a new medication versus fifty bucks a year for a conventional one. Although, in our low dose studies on conventional drugs, we didn't have the disabling side effects that everybody attributed to them. People used to visit our program in those days and our patients didn't have disabling side effects and they would say, "You're sure you're dealing with schizophrenia patients"? And, I'd say, "Yes, why do you ask"? And, they'd say, "They don't look like schizophrenia patients". I'd say, "What would a schizophrenic patient look like"? Then they would describe somebody with pseudoparkinsonism, shuffling gait and stuff like that. And, I'd reply, "No, we don't have those here." That's a long answer to your short question

AT: Let me ask you a final question. What are your thoughts on the development, diffusion and use of minor tranquilizers? Your career has kind of spanned the time frame from Miltown (meprobamate) in the fifties to Xanax (alprazolam) in the eighties?

GH: I can't say I've tracked that development. I don't agree with the attempts by States to control prescriptions like they did in New York with benzodiazepines. I know there have been abuses. There are abuses for everything. Also, there's a lot of needless suffering among people who could profit from the selective use of benzodiazepines. The problem becomes acute with people who suffer real sleep problems. That's where the biggest problem shows up and you still get physicians reluctant to prescribe non-addicting hypnotics. People I've seen who use them on a regular, not just on a prn basis, really do well. Their lives have changed around, especially, elderly people. Why not to give these

drugs to them? A bigger case can be made for a good night's sleep than any potential abuse. Sleep is very important and increasingly we're finding that in the elderly. Studies indicate they're underused more than overused. The number of people who meet diagnostic criteria for disorders in which an anxiolytic, antidepressant, or a hypnotic could be used is probably far greater than the number who use the drugs.

AT: In the early 1970's there was a lot of media attention to how addictive these drugs were and we saw harrowing scenes of women, heroin addicts, writhing on the floor in hospital wards.

GH: I never saw that. What I did see, earlier in my career, was people who used the barbiturates in excess. In high chronic doses some of the benzodiazepines with long half-lives could get you into trouble, but there are others with shorter half-lives. I've known people that have taken a medication, such as alprazolam, on a daily basis for years. If someone like that wants to come off, under medical supervision, they don't run into problems. There are people popping these pills at will. You have to watch how you generalize, to see what portion of the population taking these drugs is abusing them. You can abuse anything.

AT: Sure.

GH: Ask questions from people who are not abusing them but are regular users and see what their lives are like. This is a strange country in that regard. We're still very much of a Calvinist country. We don't want to take medicine. Most people don't want to, including myself; I'll do anything to avoid medication. I don't take, even at my age, any prescribed medications but I do take chondroitin and vitamin supplements, things like that. Most of us are still taught there's some kind of a moral failure if you rely on medication to get through things.

AT: Right. These days, taking meds is considered a crutch.

GH: Or, as I started this conversation, a "symptom cover" that keeps you from facing your real problems. I don't have any strong convictions on that one. The older I get the more I think people are entitled to a life of peace and comfort and how they get there is partly their decision and partly the medical professions.

AT: Thank you very much. It's been very helpful.

GH: You're welcome. Thank you for having me.

JOHN M. KANE

Interviewed by Thomas A. Ban
Acapulco, Mexico, December 11, 1999

TB: This is an interview with Dr. John Kane* for the archives of the American College of Neuropsychopharmacology. We are in Acapulco, Mexico; it is December 11, 1999. I am Thomas Ban. Let us start from the beginning; when and where were you born? Tell us about your education and how you got involved in research in psychopharmacology.

JK: I was born in New York City in 1945, and grew up in suburban Westchester County. My father was a physician and my mother was a buyer for the Army and Air Force Exchange Service. My father specialized in pulmonary medicine and was very influential in my decision to go into medicine. He had enormous intellectual curiosity in a variety of areas and made significant contributions to X-ray techniques and pulmonary medicine. I went to high school at the Horace Mann School in New York and attended Cornell University, where I majored in English. From there I went to NYU Medical School and became increasingly interested in psychiatry, spending a good deal of elective time working on different projects. One of these was with Neal Miller at Rockefeller University, another with Stella Chess in the Child and Adolescent Psychiatry Department at NYU and a third involved evaluating the Substance Abuse Treatment Program in a residential community model. Those experiences were very valuable in forming my subsequent decisions and perspectives.

TB: Where did you do your residency in psychiatry?

JK: I did my psychiatric training at Hillside Hospital and the reason, primarily, was that as a medical student, wandering around the bookstore and library, I came across a book Don Klein and John Davis had published in 1969 on *Psychiatric Diagnosis and Treatment* that made a profound impact. I have kept my original, underlined, annotated copy, which I started reading in medical school. Don Klein was at Hillside and that was an important factor in my decision to choose it for residency.

TB: Are we in the late 1960s?

JK: Right. The book was published in 1969. I graduated from medical school in 1971, and spent four years doing residency at Hillside Hospital. During residency, I tried to fulfill a dream I had to spend time studying anthropology and sociology. So I took graduate courses at Columbia in those departments, and they were very helpful in giving me a broader

* John M. Kane was born in New York City, New York in 1935.

perspective on factors that influence human behavior. During residency I started working with Don Klein and Rachel Gittelman-Klein in research and I'm very grateful to Don for making himself available to me as a resident. He would let me sit in on his consultations with private patients as an observer to learn from his diagnostic and treatment approach; needless to say that was a very valuable experience. Don Klein has been one of the most valuable contributors, helping to advance the field in terms of diagnostic sub-types and response to pharmacologic agents. Having that perspective as a resident was extremely valuable and made me more and more interested in research. So when I finished residency in 1975 I began working full time in research, not only with Don but also with Arthur Rifkin and Fred Quitkin; they also were extremely generous. They treated me as a peer rather than a resident and made me feel I was an equal member of the team. Beginning to spend full time in research in 1976, with another colleague I started the Lithium Clinic at Hillside Hospital. We did a number of very large treatment studies in unipolar and bipolar depression, subsequently, published in the Archives of General Psychiatry. A lot of that research was done under the leadership and guidance of Fred Quitkin, Arthur Rifkin and Don Klein. So, during the first couple of years of my residency, I was heavily involved in affective disorders, particularly bipolar disease, becoming an expert in the management of those patients. We ran over a hundred and fifty patients through long-term clinical trials, involving lithium, imipramine and, in some cases, placebo. After that Don and his group were recruited to Albert Einstein by Ed Sachar and, then, to Columbia. I had a choice as to whether to go with them or stay at Hillside. That was probably one of the more difficult career decisions I ever made, because I knew I was not ready to go it alone. Don Klein made the decision easier by telling me if things didn't work out at Hillside I would be able to move to Columbia. For the next year or two I continued to meet, quite frequently, with Fred Quitkin, Art Rifkin and Don to get their advice but, within a couple of years, I was able to get my first NIMH grant, examining the dose response relationship in long term maintenance treatment. The idea was of using antipsychotic drugs to prevent relapse in patients with schizophrenia. We did some pilot studies first, which suggested that extremely low doses of antipsychotic medication could be effective and then set up a large controlled trial, which involved about one hundred and sixty patients.

TB: When you say extremely low doses of antipsychotic medications could be effective, what do you mean?

JK: Fluphenazine decanoate, 1.25 to 5 milligrams every other week. At that point in time, there had not been a lot of work on trying to establish minimum effective doses for maintenance treatment. One of the incentives was to reduce some of the long-term side effects that had been associated with antipsychotics, specifically, tardive dyskinesia (TD.).

TB: So you were interested in reducing the occurrence of TD. Could you tell us something about TD?

JK: TD is a syndrome that was observed shortly after the introduction of antipsychotic drugs, in the mid to late 1950's. It involves abnormal involuntary movements, usually of the mouth, tongue and face, but often involving the extremities as well. In its' most severe form, this could be disfiguring and disabling. In some cases it was persistent for years even after the antipsychotic drugs were discontinued. Initially, there was debate as to whether or not this condition was due to antipsychotic drugs, but it became clear, over time, that the drugs were playing a major role in causing this condition. A major goal in psychopharmacology, in that era, was to see if we could reduce or eliminate the risk of TD. Our desire to identify minimum effective dosages for maintenance treatment was, to some extent, driven by concern about TD. We did show, using these micro doses, we could produce a significant reduction in the early signs of TD. On the other hand, the risk of relapse did go up on the small doses we used, although the relapses were not usually severe and did not, necessarily, require hospitalization. There was a balance of risk to benefit when one begins to approach the minimum effective dose. We went on to do a number of studies, including participation in a large NIMH funded multi center project, called Treatment Strategies in Schizophrenia in which Hillside was one of five sites. Another area we began work on was first episode schizophrenia. There had been very few studies focusing on that population. We knew antipsychotic drugs were very effective in controlling the acute signs and symptoms of schizophrenia, but it was not clear whether one needs to continue treating patients over a long period of time after recovery from a first episode. In collaboration with Fred Quitkin and Arthur Rifkin, we published a paper from a placebo controlled maintenance trial in first episode patients. We demonstrated there was a significantly higher risk of relapse among patients assigned to placebo than among patients continued on active drug. The trial lasted for a year. The sample size was relatively small, twenty-eight patients, but we were able to show a significant difference. It was the first controlled trial on maintenance treatment of schizophrenia. In spite of the fact we and others have shown that the relapse rates, after five years, among

untreated patients was as high as eighty percent we are still struggling to get patients to accept continuation of medication after remission from a first episode. The results from the most recent study at Hillside suggest that medication can reduce the risk of relapse by a factor of at least four and is the single most important factor. In our first episode maintenance study, it turned out that patients with poor pre-morbid social adjustment had a much higher rate of relapse when they went off medication than patients who had better social adjustment. In the early 1980's, when I recruited Jeff Lieberman, we continued with studies in first episode patients, following them longitudinally and looking at issues such as brain morphology, cognitive functioning, neuroendocrine response, treatment outcome, relapse and so forth. In the late seventies there were a couple of other areas we were actively pursuing.

TB: Didn't you continue with your research on TD?

JK: We did. Jim Smith and I wrote a very extensive review on the prevalence of TD, which was published in the Archives. It pointed out that the estimates of the prevalence of TD ranged from half of one percent to as high as fifty-six percent. That made it clear there was a lot of uncertainty as to how serious a risk TD really was. So, we decided to start a prospective study of TD. Many people said it was overly ambitious to try to follow patients longitudinally to determine whether they would develop tardive dyskinesia, but we had the necessary population and infrastructure at Hillside. We were also able to win support from NIMH for a very large scale prospective study of TD development, which went on for more than a decade. Findings of our study suggest the incidence of TD grows with cumulative antipsychotic exposure by about five percent annually. We identified some risk factors for developing TD, for example early EPS. We also demonstrated that patients with depression, particularly unipolar depression, were at greater risk for developing TD. There's still a debate about whether bipolar diagnosis is also associated with a higher risk. We did not find that, but we did find that lithium, when given concurrently with antipsychotic drugs, confers some protection against tardive dyskinesia. The rationale for that is lithium's ability to reduce the hypersensitivity of dopamine receptors. That prospective study of TD was rather unusual and did provide very valuable data for both investigators and clinicians.

TB: Could you elaborate on what kind of valuable data it provided for investigators and clinicians?

JK: It provided valuable information, for example, relevant to informed consent. In the area of TD the simple fact of being able to say that the risk for developing it is five percent over time, is helpful in discussing the

risk-benefit ratio of treatment. It was also important feedback to those involved in drug development by underlining the need for compounds that would have a significantly reduced risk for TD.

TB: So this is how you got involved in research with clozapine?

JK: The next area of research we got involved with was with clozapine, a so called atypical antipsychotic drug, which had been around for awhile, but had not been marketed because, in the mid 1970's, there were several fatal cases of agranulocytosis in the course of treatment As a result, a conclusion was drawn that clozapine appeared to have a significantly higher risk of agranulocytosis than conventional antipsychotic drugs, such as chlorpromazine, which was known to produce agranulocytosis rarely. In the early days of chlorpromazine treatment people used to do blood tests because of that risk but, subsequently, it was concluded that agranulocytosis was so rare it was not necessary. Clinicians were also aware that patients could recover from agranulocytosis with withdrawal of the original medication and appropriate medical management. When clozapine appeared to have a significantly higher risk of agranulocytosis its' marketing was curtailed but even in those years it was available in some countries with the necessary precautions.

TB: How did you actually get involved with clozapine?

JK: In about 1977, I was approached by Sandoz, currently known as Novartis, to take over the management of a group of patients who had been receiving clozapine from Nathan Kline.

TB: So that is how you got involved with clozapine?

JK: We had read about clozapine and felt it did differ from other antipsychotic drugs in its ability to produce a range of clinical effects, which seemed broader than other antipsychotic drugs; it seemed to be helpful in some patients who had not done well on other drugs. The main characteristic of the drug, universally agreed upon, was a very, very low propensity to induce Parkinsonism. That we found very intriguing, because we assumed that drug induced Parkinsonism was an intrinsic character of all effective antipsychotic medications. Clozapine really set a new standard in that regard. Chemically it is not that dissimilar from some tricyclic antidepressants, but it did have novel receptor binding characteristics, in that it bound to a broad array of receptors, including serotonin, α adrenergic and histaminergic receptors, as well as dopamine receptors. At that time we were aware of the different subtypes of dopamine receptors that clozapine was subsequently shown to bind to. So, it did appear to have a number of novel properties. Also it did not elevate prolactin and seemed to be more effective in improving negative symptoms, although that was anecdotal at the time. It is

relevant to the story that in the late 1970's, we at Hillside were one of the few sites in the United States using clozapine.

TB: So, Sandoz contacted you to take over Nate Kline's clozapine treated patients and do what?

JK: What Sandoz wanted was that I try to discontinue clozapine in the patients because there was no IND for clozapine at that time. We took on the challenge but, when we tried to discontinue clozapine in a number of patients, the consequences were unfortunate. I regret having attempted to do that, but we really did not know what to expect. What happened was that the first couple of patients suffered very severe relapses and we had to hospitalize them. We tried numerous other medications but none seemed to help. So, we put them back on clozapine and both the nurses and attending staff were very impressed with the results. This experience changed my attitude towards the possibility of having a differential response to antipsychotic medications. We had all grown up with the notion that antipsychotic drugs were interchangeable, in terms of clinical effectiveness. There had been about a hundred studies comparing chlorpromazine and trifluoperazine to other drugs in the acute treatment of schizophrenia and only one out of a hundred studies showed a difference, which is something you can get by chance. So, we assumed the drugs were equally effective in group comparisons but clozapine seemed to hold the promise this might not be the case. Our experience with the first few patients we took off clozapine had a dramatic effect on me. I became so interested in clozapine that we began to treat some patients, who had failed to respond to other drugs, with it. By the time we had an IND Sandoz had established the fact that agranulocytosis was generally reversible if the drug was promptly stopped. It was also recognized that, if proper medical management was provided, mortality declined substantially. I thought if it could be shown that clozapine had some unique or superior properties in comparison to the available medications it would be an important addition to our treatment armamentarium. We had a number of meetings with the Food and Drug Administration about our interest. At the first meeting we talked about some of the anecdotal data that was available and suggested this drug might hold promise for some patients with treatment refractory schizophrenia. The decision was that the FDA would consider approving this drug for marketing if, in the context of a prospective well designed study, we could demonstrate clear superiority over an available control drug. We took on that challenge and I became the lead investigator in designing and implementing a large multi-center study, funded by Sandoz, in hospitalized treatment

refractory patients who had failed multiple other drugs and also failed a prospective trial of six weeks treatment with haloperidol in doses of up to 60 mgs a day. They were patients who had been chronically institutionalized, for whom clinicians and expert psychopharmacologists had nothing to offer. We published the results in the Archives in 1988. The design was very conservative and very strict. Reading our results, most people were surprised that clozapine was able to show superiority in this population. But it did and those results led to the FDA approving clozapine for marketing in 1990. That certainly is a study I'm extremely proud of. It's one of the most frequently cited papers in psychiatry over the past decade and I think it played an important role in setting the stage for a new generation of drugs. Clozapine did serve as a prototype for a new generation of drugs to be developed. Our findings suggested it was possible to have an antipsychotic medication that caused relatively few parkinsonian side effects and was superior to other drugs in certain types of patients. The findings were attributed to clozapine's novel receptor binding profile. It also had an important heuristic impact on the field by suggesting we might be able to develop other compounds that could mimic clozapine's novel properties.

TB: What about the use of clozapine in other patient populations?

JK: Since the time of our first study we have done other NIMH supported studies in which we compared clozapine with haloperidol in less severely ill patients who live in the community and our findings will be coming out in the Archives sometime next year. In this population, we also demonstrated the superiority of clozapine over haloperidol for positive but not for negative symptoms. We are finishing a double-blind comparison of clozapine and risperidone in patients who live in the community and we already know that fewer patients are dropped for lack of efficacy in the clozapine group in comparison to the risperidone group. Interestingly, some of the risperidone patients do well and if we look at those patients who survive in the study, in terms of psychopathology, the risperidone patients although there are fewer, are doing just as well as the clozapine patients. At this point it remains an open question whether the new generation drugs can show advantages in treatment refractory patients. My read of the literature, as of December 1999, would be that clozapine would still have to be ranked as the number one drug, in terms of effectiveness in treatment refractory patients. It may be that drugs like risperidone and olanzapine also have some advantages over conventional drugs, such as chlorpromazine or haloperidol, but not quite to the same degree we see with clozapine. So we continue to do studies with clozapine, trying to delineate the areas in which it is most effective.

We also did studies using clozapine to treat patients with severe TD or tardive dystonia and found that clozapine was not only helpful in preventing TD, because of its' low risk of extrapyramidal side effects, but was also in ameliorating abnormal involuntary movements in those very severe cases in which they persist after discontinuation of antipsychotic drugs. For some time clozapine was the standard treatment of patients with Parkinson's disease that develop L-DOPA induced psychosis. Now, some of the other new drugs are beginning to play a role in that area. I should point out that clozapine is probably still underutilized. Many clinicians don't take advantage of the opportunity to switch to clozapine when other neuroleptics, like olanzapine and risperidone do not help.

TB: We have been talking about clozapine for some time but I don't think you have mentioned the dose you have been using.

JK: In the original multi-center clozapine study we published in 1988, the dose of clozapine averaged about 600 milligrams a day. Now, we usually shoot for a dose of about 500 milligrams per day. European investigators tend to use lower doses, and that still remains an area of controversy. My read of the literature, and this includes data from the clinical studies as well as studies which employed blood levels of clozapine, is we probably want to shoot for a dose of 450 to 500 milligrams a day to make sure we have an adequate trial. But if a patient doesn't respond we should do a blood level and, if the blood level is low, we should try even higher doses because once someone has got to the point of needing clozapine, we should make sure they have an adequate trial.

TB: Did you try to correlate blood levels and receptor binding?

JK: We do blood levels if a patient hasn't responded to clozapine. We don't do them on a routine basis. The studies that have been done have correlated blood levels with clinical response. They have not always been correlated with measures of receptor binding in the central nervous system. But the results support the fact that clozapine does have some unusual characteristics.

TB: At the beginning your interest was on the effect of clozapine in chronic patients, refractory to other drugs. But didn't your interest shift to studying the effect of these drugs in acute patients?

JK: We are now comparing two of the new generation drugs, risperidone and olanzapine, in first episode patients. Most of the studies were conducted to obtain new drug approval from the Food and Drug Administration in relatively chronic patients who've had multiple episodes. If you look at the literature, on average, patients are in their late thirties and they've had more than five or six previous hospitalizations with a mean length

of illness of over fifteen years. If we believe that these new antipsychotic drugs have novel properties, it's going to be very important to assess their impact at the onset of the disease and, subsequently, in patients who've not been treated with other antipsychotic drugs, so we can see the true impact of these drugs in terms of the evolution of negative symptoms, cognitive dysfunction or even brain morphology. The current study is an attempt to look at these issues longitudinally, and to begin to collect data for answering these questions. We also need data as to whether there are meaningful differences between the new antipsychotic drugs. They all seem to be effective. They all seem to have less extrapyramidal side effects in comparison to drugs like haloperidol. Whether they prove to be significantly better in terms of the course of the illness, compliance with treatment and in relapse prevention remains to be seen.

TB: Any other area of research you would like to address?

JK: In the Hillside First Episode Studies it appeared that patients, who had delay in treatment during their first episode, seemed to have a poorer response subsequently. Similar findings were reported by Eve Johnstone and by Phil May as early as the 1960's. This has led to a tremendous interest in reducing the time between onset of illness and initial treatment. It has also become clear there are prodromal signs and symptoms in many cases of schizophrenia including symptoms like depression, social withdrawal, suspiciousness, sleep disturbances, irritability, bizarre behavior and ideas of reference. None of these symptoms would allow full diagnosis of schizophrenia, but when patients and families are interviewed, it's clear in many cases, there are early signs before the onset of full blown psychosis. The question now becomes, can we with certainty, identify people in the prodrome and institute effective treatment that might reduce the risk of a full blown psychosis? Hillside has now established a clinic which focuses on this area of research.

TB: So there are certain manifestations that might be predictive for developing psychosis?

JK: Identifying these prodromal signs and symptoms does have some predictive value. If you combine that with family history you're increasing the predictive power to justify routine treatment. We're beginning, in some cases, to use antipsychotic medication if we are seeing early psychotic signs and symptoms. We are also trying to identify social and environmental factors that play a role in delay of getting treatment. We have to do a much better job of training primary care physicians, other health professionals, and even general psychiatrists in rapidly

and reliably identifying the early signs of schizophrenia, making sure patients get into an appropriate treatment setting to manage that phase of the illness. The public also suffers from the fear and stigma associated with mental illness, so even when a family is concerned about a young person demonstrating some worrisome or bizarre behavior, they may consciously or unconsciously deny that, because they're fearful of the consequences. We need a tremendous amount of public education outreach to physicians, clergy and school teachers to narrow this gap.

TB: Any other area of research you have been involved with?

JK: There are a number of other areas. We've been involved in a number of clinical trials, developing new compounds. Another area is the issue of involuntary commitment. We published a paper a number of years ago on what happens to patients' attitudes after involuntary commitment to hospital. We found that once patients responded to treatment their attitudes towards involuntary hospitalization changed. In response to a series of questions, most patients said if this ever happened again, they would want you to do the same thing, which is very important, because when we discuss the issues of protecting their civil liberties and protecting them from harm it can be a very difficult balance. There are patients providing proxy consent, so if they do become psychotic they're giving permission to be hospitalized. That study was very helpful, in clarifying that patients were capable of understanding and appreciating the need for hospitalization. The other striking finding was that the overwhelming majority of patients, despite having been committed to the hospital on an involuntary basis, once they're out of hospital, did come back for treatment on a voluntary basis over a long period of time, which suggests that they recognized and accepted the need for treatment. Another area that we've been interested in and concerned about is the placebo response in schizophrenia. There's a lot of debate as to whether there should be placebo-controlled trials in any condition for which there's an effective treatment available or should we just do active comparisons. I think there are very legitimate points to be made on both sides, but one of the realities in schizophrenia research, involving affective disorders, is that response to treatment of proven effective antipsychotic medication is very heterogeneous and very unpredictable. We recently conducted a meta-analysis, involving hundreds of patients participating in controlled clinical trials, comparing proven effective antipsychotics and placebo for some of the new generation drugs, and what we showed was there was an enormous variability in the placebo response during the course of a four to six week trial. We also have historical data that shows an enormous variability in response

to haloperidol during a similar four to six week period. All in all it can be difficult to draw conclusions without a placebo group. On the other hand, there's legitimate concern about participation in a placebo controlled study when effective active treatments are available. I think it requires a consensus among patients, families, investigators and governmental agencies, as to what's necessary scientifically and ethically appropriate. That debate is still going on.

TB: Could you tell us something about the different assessment instruments you are using in your research?

JK: There have been a number of scales developed over the years to measure different aspects of psychopathology. There's also a group, including Nina Schooler who we recruited to Hillside a couple of years ago, working on a new scale which will hopefully be an improvement over previous scales in measuring both positive and negative symptoms. Rating scales have played an important role in helping to define clinical response, but they have been somewhat disappointing in capturing the array of domains in which patients with schizophrenia are affected. The field is still struggling with trying to develop a comprehensive set of instruments that would include both positive and negative symptoms as well as cognitive functioning, psychosocial symptoms and other factors relating to long term functional outcome. We've primarily utilized the BPRS. Peg Werner and others developed the BPRS' Hillside version. We have a whole research unit focusing on that area. We're pleased with some of the results we see in the changes in psychopathology in short and long term clinical trials, but the real question is whether the patient can function in the community in a relatively normal way.

TB: What would you consider as your most important contribution to the field?

JK: Probably my work with clozapine in demonstrating how important clinical research can be in developing newer and better treatments and also in playing a heuristic role for research on a pre-clinical level. We'd like very much to be at a point where the etiology and pathophysiology of the disease are driving the development of treatment, but we're not there as yet in schizophrenia. So we rely on clinical research and observations to establish advances in treatment and try to reason backwards from there to try to understand what implications this might have for mechanisms of action, pathophysiology and so forth. Unfortunately, very high quality clinical research is not given the recognition and support it needs. I hope one of my major contributions through the clozapine or prospective studies of TD, or the first episode studies, would be to demonstrate how valuable well designed, carefully conducted clinical

research can be in setting the stage for further advances in knowledge, whether clinical or pre-clinical.

TB: Is there anything specifically you would like to see to happen in your field of research?

JK: We have not succeeded in understanding the mechanism of action of clozapine and there's a tendency to focus rather narrowly, on a number of different neurotransmitter systems involved. By doing that we often arrive at premature closure. Also, it may very well be that schizophrenia is a number of different diseases and we still have a long way to go to understand the sub-types and different domains affected. It may very naive to think one drug is going to simultaneously improve positive and negative symptoms, cognitive dysfunction, social withdrawal, apathy and lack of motivation, that all of these will be alleviated by a single drug. It may be we need multiple treatments and not just pharmacologic ones but also psychosocial treatments to be able to address all the domains of dysfunction we see in this disease we call schizophrenia. That's another area we hope we've made some contribution.

TB: So, you would like to see a more comprehensive approach to treatment?

JK: Right. We've recently recruited Anil Malhotra, who is focusing on genetic strategies to delineate sub-types and better understand pharmacologic response. The enormous excitement surrounding mapping of the human genome and explosion of knowledge that will take place in the genetic underpinnings of disease and pharmacologic response, is going to be one of the most exciting areas over the next decade.

TB: At the beginning of this interview you talked about Don Klein, and later on you mentioned Jeff Lieberman. It seems Hillside provided a stimulating environment for research.

JK: Certainly, Hillside provided a stimulating environment for research. I talked about the role of Don Klein and other colleagues and that, in the early 1980s, I recruited Jeff Lieberman. I was able to sponsor a research scientist development award for him in the mid 1980's, which enabled him to begin the new generation Hillside First Episode Studies. And Jeff continued that work for more than a decade at Hillside.

TB: Didn't Jeff work with you on methylphenidate? Could you elaborate on that?

JK: One of the issues has always been can we do a better job of predicting drug response or vulnerability to relapse? There was still considerable debate about whether maintenance treatment should be on a continuing or intermittent basis for some patients. We thought if there was some way to predict who might be vulnerable to relapse we would know whether to make a concerted effort to keep a patient on

medication. There were observations that dopamine agonists, given orally or intravenously, were capable of producing a transient exacerbation in psychotic signs and symptoms and this was a methodology for identifying those vulnerable to relapse. I think the whole area of challenge studies has come under question as to whether or not that is something we should be doing, but these studies were done at a time when it seemed an opportunity to help by establishing a better profile of what the risks and benefits of treatment would be. It was also applied in the first episode study as an attempt to understand the sub-types of patients who might respond better or worse to treatment.

TB: You found clozapine superior to some of the other neuroleptics and especially to haloperidol. Did anyone replicate your findings?

JK: There have been a number of controlled trials with clozapine, conducted by Alan Brier, Sanjiv Kumra, David Pickar, and very large scale studies, conducted by Bob Rosenheck and Susan Essock, but the results are not always the same. Some studies have demonstrated clear superiority in measures of psychopathology, whereas other studies have shown superiority in rates of relapse or rehospitalization. But the superiority of clozapine has held up well across a number of studies. The irony is that there's not as many double-blind control trials on clozapine as there should be and a lot of the claims that have been made for clozapine have come from open and uncontrolled trials, so there's still a lot that needs to be done.

TB: Let me switch to some of your publications. You started to publish in the late 1970s, didn't you?

JK: There were a couple of papers that came out around the same time about the prophylaxis of unipolar and bipolar depression; it was one of my first major publications in the Archives. Data from our first episode maintenance treatment study was an early report. Our work on the prevalence of tardive dyskinesia was also an early report.

TB: Were these papers published in the late 1970s?

JK: Late 1970s and early 1980s.

TB: What was your last publication?

JK: The last publication is one that's in press, which will be a report on the Six Month *Comparison of Clozapine and Haloperidol in Moderately Ill Outpatients*. That's the last paper in press, right now.

TB: Approximately how many papers did you publish?

JK: About two hundred papers and a few books.

TB: Were any of the papers or books translated from English into other languages?

JK: I think some of the papers have been and the 1988 clozapine paper has something like seventeen hundred citations, so it's a citation classic, which I'm very proud of.

TB: You are the recipient of many awards. Didn't you recently receive the Heinz Lehmann Research Award?

JK: I was very pleased to receive that. Heinz Lehman was one of the pioneers in our field and it was a great pleasure to receive something with his name on it, particularly since I'd had the pleasure of knowing him. He was at the award ceremony. I've been very gratified to win a number of awards, including the Lieber Prize and the American Psychiatric Association Research Prize. I never expected any of those things when I went into research. It was purely a fascination with the challenge of trying to improve the treatment and it's always been a privilege to work in this field and be recognized for contributions.

TB: Is there anything we left out and should be on the record?

JK: The other thing I'm most proud of is that, for the past twelve years, I've been chairing the Department of Psychiatry at Hillside Hospital, one of the largest psychiatric hospitals in the country and that has a very strong research and clinical training tradition. I'm very proud of the fact we've been able to integrate research into a private, not for profit, psychiatric hospital, and to train a terrific group of clinicians and investigators as well as maintain a resource for people in the community and nationally in need of treatment. Probably the most gratifying is the acknowledgment and gratitude from patients and families helped by our work.

TB: So you have been active as a clinician, teacher, researcher and administrator?

JK: Unfortunately, a few years ago, I made the decision to curtail my clinical practice, and so I'm seeing a very small number of patients now. But, as a clinical administrator, I'm involved in trying to provide state of the art care to thousands of patients, so I feel much rewarded by that.

TB: I think we should conclude this interview on that note. Thank you very much.

JK: Thank you very much.

MARTIN M. KATZ

Interviewed by Jean Endicott
San Juan, Puerto Rico, December 14, 1995

JE: I'm Dr. Jean Endicott and I'm interviewing Dr. Martin Katz,* who's been a member of ACNP since 1963. Now, Dr. Katz, what field did you start out in?

MK: I got my basic education in chemistry, went into psychology in graduate school and received my degree in psychology at the University of Texas. So, I had an interest in these two disciplines for quite a while.

JE: How did you get into your current field?

MK: Into psychopharmacology?

JE: Right.

MK: After graduating from the University of Texas, I worked there for a year on research as a post-doctoral fellow. The project had to do with the effects of Vitamin C on intelligence, a study I was very skeptical would result in any positive results, but it was a nice position. I had run into Jonathan Cole at a scientific meeting in Texas, and he was impressed with the design of that study, because it was so much like a drug study. He was on the verge of taking over a large program at the National Institute of Mental Health on a new discipline called psychopharmacology, so he was seeking people who had done things like this or might be interested in that field. That was the last I saw of him for awhile. But shortly after completing that post-doc I went to Washington to work in the Veterans Administration Neuropsychiatric Laboratory. There I got involved in a project evaluating the outcome of psychotherapy and worked with Maurice Lorr, who was expert in development of quantitative rating scales for symptomatology. This is back in the late 1950s, and was a new research area at the time. And, I came across Dr. Cole there again. It turns out he was in charge of something like a two million dollar project by way the National Institute of Mental Health to promote this new discipline of psychopharmacology. All this happened because of excitement over the discovery of the new drugs for schizophrenia that was provoking a revolution in our field. They apparently couldn't give him enough money to get that program started. I was viewed as a young researcher, but I had the skills he was interested in. He was hiring people, so he brought me to NIH. I was recruited in 1957 as the Executive Secretary of the first Psychopharmacology Advisory Committee. I must have been thirty years old at the time and I was

* Martin M. Katz was born in New York City, New York in 1927.

confronted with relating to all these senior scientists in the field from all over the country. So, it was a very exciting prospect.

JE: What was the reaction to having a psychologist head of that?

MK: I don't think there was any concern. These were the people going to put this new field together so the committee was made up of representatives from several disciplines. Psychopharmacology, by definition, involved psychiatry, chemistry, pharmacology and psychology, so the mix of people involved was from all of these fields. They might come from whatever direction in the sciences. That was not unusual.

JE: What were some of the first programs you were involved in?

MK: The entity was called the Psychopharmacology Service Center (PSC) and the mission was to get out into the field and to develop this new discipline. That meant providing investigators with funds to develop programs in basic research on the new drugs and, in a parallel fashion, to attack the problems of clinically evaluating the new drugs. Despite knowing the drugs worked and, having seen them do so in small studies, they needed definitive evidence on large representative samples around the country that the drugs were effective. So, the second part of the program had to do with what they called Collaborative Multihospital Clinical Programs for the evaluation of these new drugs. To Jon Cole's credit he was able, with the help of his staff, to launch these studies. They were the first collaborative studies ever launched by NIMH to investigate this kind of issue, which is the evaluation of psychiatric treatments. So the Center staff had to be concerned about issues in both basic and in clinical research.

JE: Do you remember who some of the people in the field were back then?

MK: The Chairman of this advisory group was Ralph Gerard, a nationally known neurophysiologist from the University of Michigan. In psychology, it was Howard Hunt, Columbia University. In biology and psychiatry, it was Seymour Kety. Nathan Kline, a clinical researcher, was one of the real movers in the field; he helped generate the funds for the program. Louis Goodman, Chairman of Pharmacology at University of Utah, was the author of the most prominent text in clinical pharmacology. These were much respected people and they were, because of the funds and new opportunities, as excited as everybody else about this field.

JE: Could you tell us something about what your career was and what you did in relation to that?

MK: I was Executive Secretary, which meant active involvement in the review of grant applications and support of some research programs in my area of work. Then, after almost two years in that position, I went back into

active research at the Center. I worked with the collaborative programs that had begun to develop methods of evaluation. I was given the task of developing a methodology for evaluating the long-term effects of these agents once the patients when they went back into the community; how long did the early positive effects last. That was a major issue and I developed a method for measuring clinical and social adjustment in the community. They were called the Katz Adjustment Scales and they're still in use. On an analogous issue there was short-term evaluation of the drugs. Having come out of the laboratory in the VA, I was very familiar with those techniques and helped put them together for that large-scale study. So, I worked on that part of the study and also on issues around psychedelic, LSD type drugs. These drugs were also a major issue. When the field started we had this parallel development of "good" drugs, the tranquilizers and antidepressants, the ones supposed to solve mental disorder, and "bad" drugs, the psychedelics. The latter were capable of disrupting the "personal psyche" and the whole community. I was given responsibility for following up on those drugs, accumulating scientific evidence on their actions and impact. After doing that for a few years, I was appointed head of a special studies section for psychopharmacology. It gave me the opportunity to develop a laboratory that would look more intensively at LSD type drugs. With a small staff I developed a laboratory in a prison to look at new methodologies for studying how they worked. At first, for safety, we experimented with small dosages to see the early psychological effects. Later we expanded these studies and managed to get a number of other investigators involved. So, this research grew into a major program, in parallel to what was going on in the community, with funds increasing every year. I was heavily involved from about 1963 until 1968. Then I was able to follow another interest I had, the influence of culture as a variable in drugs effects, and more generally as a factor in the expression of abnormal behavior.

JE: Expression of abnormal behavior?

MK: Right. Also, I got involved, by way of that special studies group, with the broader issue of classification of disorders. We mounted a very large national conference in 1965 that resulted in a book on *Classification of Mental Disorders* designed with Jonathan Cole and Walter Barton, who was head of the American Psychiatric Association. That national conference identified some of the major problems confronting the field with regard to diagnosis, which I would be involved in later.

JE: What were the drugs that you worked with, other than LSD? Were they mainly antipsychotics or were you, also, involved with the antidepressants?

MK: During the 1960's mainly antipsychotic drugs. I had done a lot of work on the phenomenology of schizophrenia, on the effects of drugs on schizophrenia, by way of the quantitative rating methods developed during that time. That was my main area of work. Then, in the studies with LSD we used amphetamine and chlorpromazine as controls. Those lines of research ran parallel, they didn't cross.

JE: Were you using videotape technology back then?

MK: No. I wasn't involved with that at that time.

JE: So, you moved into the issue of cultural expression and the response of different ethnic groups to treatment. Could you say something about the project?

MK: I spent 1968 at the University of Hawaii in Honolulu on a Fellowship from the Mental Health in Asia and the Pacific Program. I took some of the rating methods we'd developed for clinical drug trials to apply to the issue of whether psychosis in Hawaii-Japanese and Hawaii-Caucasian schizophrenic patients was expressed differently in symptoms and social behavior. Hawaii was a great laboratory for examining the effects of ethnic influence on behavior, so it was part of the reason I was sent there. We worked out a research program for doing that at the State hospital. We started research and I did get involved in videotaping about that time, because we were attracted to the possibility of demonstrating the differences in pathology in a more open way, so that people could see it more clearly than by just extracting information from the scales you and I are very familiar with. I was there for a year; greatly stimulated by the East-West Program on Mental Health in Asia and the Pacific. The NIMH, in the meantime, had changed structurally, under a new Director. Psychopharmacology became a branch. The new NIMH director was Stan Yolles, and they had redesigned how they were going to support research in the future. As part of the reorganization they created a new Clinical Research Branch and had a chief of it for about a year. He, however, ran into some difficulty and decided to leave. This was a new branch with a whole new mission. Lou Wienckowski, who was the director of the division of extramural programs, offered me the position of Chief of that branch which brought me back from Honolulu. That branch had a direct line to psychopharmacology, because what psychopharmacology had accomplished was to make us all aware we had to do a better job of evaluating treatments. It sounds very strange, and you'd think we were well equipped to do that kind of thing by then. But it was the sixties and there were very few people who had a strong psychometrics orientation or who were in a position to develop the kind of instruments capable of sound tests of whether one treatment was

better than another. The kind of background I had made it easier for me to go into the general field of clinical research. Psychopharmacology still figured strongly but in clinical research proper we would have to look at the world differently. The broad field of clinical studies was partitioned into a program on depression, one on schizophrenia, a program on psychosocial treatments, a program on basic psychopathology and one on biological factors in mental disorder. After I became Chief of the Branch, we developed "focused programs," as for example, the program on depression and psychosocial treatments. Then we began programs in psychopharmacology that had thrusts in two directions. We had to promote and support investigators in the field who could develop methodologies we needed and also promote the general field of clinical research. To do that we had to stimulate the field by way of conferences and support of collaborative research. In many ways it was a direct extension of what we had been doing in psychopharmacology. I never left psychopharmacology as a specialization, I just extended my interest. I still came to the ACNP meeting every year, regardless.

JE: When you took over as head of the Clinical Research Branch, do you remember what the budget was?

MK: It must have been in the area of about five million dollars.

JE: And that was the period when it was growing fairly rapidly.

MK: By the time I left, which was ten years later, it was somewhere in the range of twenty to twenty-five million dollars, so, it had gone up rapidly during those years. Those were good days for mental health research. Psychopharmacology had a lot to do with stimulating support for all areas of our field and we appreciated that. In that ten-year period we had several stimulating conferences. In 1969 there was the well-known Williamsburg Conference, which highlighted depression and the very exciting work on neurochemical theories of depression, the so called catecholamine hypothesis of affective disorders identified depression as a derangement of central neurochemical systems. The work had grown out of psychopharmacology, because the discovery of antidepressants opened up the issue of how these drugs were working. The drugs appeared to be changing functioning in certain neurotransmitter systems and investigators were able to associate the changes with depression. It looked as if we were very close to learning what the biochemical source of the depressed condition was. But you couldn't arrive at a definitive answer unless you did clinical studies, which were sound methodologically, and had the proper breadth and reliable diagnostic information. So, it raised the question of how to achieve a clinical study with a sufficiently large and diverse sample to

test the biochemical hypothesis. And the need for such a study was one of the conclusions of that conference. But, the real issues identified as important to resolve, before the field could go forward, were three. One was confusion over diagnosis. At that time, there were several diagnostic systems and people argued about them continuously. You couldn't compare the results from one study to another because of the different diagnostic systems they used. Out of that discussion came a recommendation that we develop a more reliable nosological system for research purposes. The second issue had to do with pursuing ideas about the genetic basis of the disorders, and the third had to with testing, in a definitive way, the exciting neurochemical hypotheses. From that meeting, where we had some of the best minds in the country, a set of recommendations were developed with the idea that we generate a collaborative study. But before that occurred, something had to be done about upgrading the methodology to be used, particularly for diagnosis. You might remember this very well because you were one of the key figures we turned to. After the meeting we asked Bob Spitzer and your group, with Eli Robins, from St. Louis to "collaborate" and clear up the methodology relevant to diagnosis.

JE: Believe it or not, we did.

MK: First we had to refine the "Research Diagnostic Criteria", because we wanted to have diagnoses that met research standards for reliability so that a clinician in Iowa wouldn't be collecting data in a different way than a clinician in New York. So you and your group were commissioned to develop a standardized data collection instrument. After getting that done, if we had stopped we would have accomplished a lot, because those instruments you, Bob Spitzer and Eli Robins developed, the RDC and SADS, have been used by almost all investigators for the past twenty years. It upgraded quality and helped make collaborative studies possible. Now we could proceed to test ideas about the neurochemistry of depression and the role of genetics. We organized another conference on the psychology of depression so we could better study the principal theories and psychological phenomena in depression. That also was a successful conference and was followed, as was the biological conference, by a published book. The title of the first book on the Williamsburg Conference, edited by Williams, Katz, and Shield was, *The Psychobiology of the Depressive Illnesses*; and the title of the second book, edited by Friedman and Katz was, *The Psychology of Depression*. Later on we attacked the whole issue of psychotherapy for depression and compared it directly with drug treatment through a collaborative study, published in an article by Waskow et al in the

Archives of Gen Psychiatry. What I'd like to point out about those initial studies, The Clinical and the Biological Collaborative Studies on the Psychobiology of Depression, was that they were the first collaborative studies. There's a question now whether similar studies will ever get done, designed to test experimental hypotheses. At that time we were familiar with the type of collaborative study intended to evaluate a treatment. We had a format for that. But we never used the methodology for a study that would go beyond treatment to test theoretical hypotheses about the causes or nature of a major mental disorder.

JE: There were other differences, too. Most collaborative projects were designed in Washington and carried out across the country. And the way you set up these new programs, there was a lot of back and forth deciding what was going to be studied. Could you describe some of that?

MK: We would bring our group of scientists and clinicians, leaders in the field, together, and they would have responsibility for designing the study. We had the staff to help and people of substantive background at the NIMH who could collaborate in the design and the work, but their status in the group was as co-investigators. The group would design the project and participate in carrying it out. To use the Collaborative Biology Study as an example, we had the expert in neuroendocrinology at one center who would take care of the laboratory work for the six participating hospitals, whereas measures of central nervous system chemistry were handled in another laboratory. The investigators who ran each study were leaders in the field, people like Peter Stokes at Cornell and Jim Maas at Yale. In St. Louis, the group would be using the most advanced equipment, mass spectrophotometry, for measuring drug concentrations in the plasma. At that time, there were only two or three pieces of that type of equipment in the entire country. The St. Louis group and Eli Robins would take responsibility for that work. We would, in Washington, take responsibility for the behavioral analysis. It was in that biological study that we instituted the video method, so that we had a pictorial record, based on the standard interview you promoted earlier for data collection. Since these assessments would be done frequently in the drug evaluation process, we developed a much briefer, simpler interview for the video work. But every patient would get the same standard interview at each assessment point. We intended to create a psychological testing instrument out of this, a standardized instrument interview and rating procedure that would be administered pre, during and post the course of drug treatment. This was a new technique added to the standard instruments, the Hamilton scale and SADS-C. So, that's

the way the biological component of the collaborative studies was conducted. Its parallel was the clinical study which investigated nosology and genetics, and had as complex a collaborative arrangement as the biological study, involving investigators from all over the country. We were quite proud of those studies. They had a lot of effect on research if you examine its impact on the scientific community, apart from the study's actual results. In a sense, the collaborative network and studies served as mechanisms for psychiatric and research training in our field. While we didn't have that many centers in the country, they could train a large number of investigators. The field was still young at that time and we like to think that people like you, Nancy Andreasen, Paula Clayton, Bill Coryell, Martin Keller, Jim Kocsis, Alan Swann, Regina Casper and Steve Secunda could go on to be leading investigators in our field. So that was a major plus for the program in a field that needed improvement in the quality of its methodology to solve the major clinical and scientific problems that confronted us.

JE: You also had skeptics who thought that it was going to be impossible for groups of independent investigators to work in a collaborative fashion. But the fact is those programs are still running.

MK: That's right. We were thinking about that at the recent memorial for Gerry Klerman, Chairman of the clinical study. Unfortunately, we also lost Jim Maas who was the moving force behind the whole biological effort. In the talks at Gerry's memorial, we realized that the leaders of these two groups had to be strong people to manage investigators who were independent leaders in their own right. The co-investigators were all very accomplished and they weren't used to working closely together with other people, who they viewed more as competitors than collaborators. So the strong leadership qualities that were necessary in a Chairman were certainly fulfilled by Gerry Klerman and Jim Maas.

JE: That was planned, on your part, carefully.

MK: You make a lot of mistakes, but in those cases we chose well. You and I know that the clinical study wouldn't have lasted three or four years if we didn't have somebody like Gerry at the helm. I feel the same way about Jim Maas who was at the helm on the biological aspects of the study.

JE: You were chief of the Clinical Research Branch of NIMH during that time.

MK: As Clinical Research Branch Chief, over that ten-year period, there was another accomplishment we were proud of. Toward the end of that tour, we managed to establish the Clinical Research Center Program. This was a kind of program the NIH supported for almost all medical

specialties but we did not have one in mental health in the early 1980's. A lot of people were very skeptical about it being a worthwhile venture. It seemed it would require large amounts of money for very broad programs of research and training when the NIMH was used to putting money in very specific, focused research programs. The latter could be monitored more easily, more effectively. But we also knew the side effects of creating these unusual programs where we were in great need of trained investigators. We needed people to have more room to develop so those centers would be a little more expensive, but we would get a lot more people into the field and a lot more problems solved. And it did work that way. I understand it is now being phased out, but I think it did great service for the development of our clinical research program for the past twenty years.

JE: I hope it's not over.

MK: I think it's close to being over because of budget constraints.

JE: What have you seen as major changes over the past twenty years in your work and contact with people?

MK: That's a difficult question but you can look at it from the standpoint of what hoped might be accomplished and what has actually happened. When we look back over the field, we see that by the early sixties, almost all the major drugs we have today had already been developed. The class of tranquilizers for schizophrenia, the class of antidepressants for depressive and anxiety disorders, lithium for mania and maintenance of bipolar depressions were all available. These were revolutionary developments. Previously there had been very little effective treatment for schizophrenia and we were losing hope. Regarding depression, we were very skeptical in this country that the disorder had anything to do with biology. It was viewed as the most psychological of our illnesses and, suddenly, these chemical agents came along and appeared to resolve in a matter of a few weeks, a condition that previously lasted a year or two. Even the psychologists, the skeptics like us, who came from the other side of this theoretical controversy, were convinced that this had a real impact. Those were major developments. The expectations were very high, that we were on the verge of getting to the sources of mental disorder, their biological basis. We began to think they were all biologically based and it would just be a matter of time until we understood how all the drugs worked. That was because all of the effective drugs were discovered accidentally but we would now be designing and creating new drugs which would be more effective, faster and so forth. We thought all of these new developments were around the corner; we would just stoke the furnace a little, put more money in

the field and get it done. And, as the field mushroomed, there were many more investigators, and much more money for development. If you look over the past thirty years, a lot has happened; plenty of drugs appear somewhat better, but until the introduction of Prozac (fluoxetine) in the early 1980's, nothing really remarkable happened. Now, some people feel these newer drugs are remarkable and I can go along with part of that, but I don't think it's the kind of development we saw with the first wave of new drugs. That's a long time between breakthroughs. Secondly, we thought that the roots of mental disorder would be uncovered and we would be able to link biological variables to mental disorder directly. In other words we would have "biological markers" for the disorders to an extent that when a patient walked into an interviewing or examination room and had blood taken there would be a test to tell us if this patient was schizophrenic or depressed. That hasn't happened. Not only hasn't it happened, we have yet to find a biological marker for any mental disorder that can be used in a diagnostic or predictive sense. Thirdly, the mechanisms of action underlying how these drugs bring about recovery are still clouded. The theories are very interesting, but we don't have definitive answers and it may be the reason we have not been able to develop new, revolutionary, drugs. On the other hand, a great deal has happened. We have struggled with these issues in the biological study of depression over many years. We're disappointed in a lot of what we were not able to find. On the other hand, we have found a few things through our work. The idea that antidepressant drugs don't impact the illness until two or three weeks pass, that widely accepted notion, is not quite true. We found that a lot goes on in the beginning that wasn't measured. The assumption of a delay is based on the fact that the drug didn't change depression as a whole without acknowledging that it did change aspects of the syndrome, for example the anxiety or anger level, very early. That may sound a small thing to make a great deal of. When investigators felt nothing happened for two or three weeks, they moved away from the notion early actions of the drug on neurochemistry were the key to antidepressant effects. So, they started to look later in the treatment process, opening up a whole new field of inquiry. We feel they abandoned, too quickly, looking at the initial stage of neurochemical changes. A lot of this controversy comes about because of the diminished role measurement of behavior has played. For some reason, behavior receded into the background with the introduction of all this exciting biological methodology. The fact that you could get a new discipline like molecular biology or neuroimaging applied to our field raised the excitement level so much that the whole

area of behavior has been neglected. Jim Maas and I worked very hard on trying to conceptualize this state of affairs that led to misdirection. We made the point that drugs don't work specifically on a disorder. That isn't part of the drug language. The language of the drug is to affect certain systems in the body, which result in changes in behavior that are specific and are going to get related to mental disorder. But the issue really is relating changes in neurochemical functioning to specific actions on behavior. We argued for trying to think in terms of neurochemical components in the action of drugs, rather than in terms of their action on disorders and diagnoses. But if we go to the trouble to get down to such refined intricate biological measurements we should be doing the same thing in the sphere of behavior.

JE: Phenomenologically.

MK: Right, if we want to solve that problem.

JE: So, where do you think we're going?

MK: We've all gotten a lift from the fact that studies that went on for thirty years to do with measuring neurotransmitter metabolites in CSF or urine or plasma, were all attempts to measure what's going on in the brain indirectly. It was very difficult work and it made some progress. But the real steps will be taken when we can measure brain functioning directly. With all the advances we should expect to see a little more rapid movement now. It appears to be moving along a little bit faster. If the behavioral side can be handled better in the future, by utilizing experts who can do this work carefully, we'll be able to connect up a lot more quickly in the future. What we want to know about the source of mental disorder is how does it come about? We have to acknowledge that although we have thousands of research articles we haven't quite got there yet. We know very little about the biology of the disorders and that's the big issue. The other big issue is how these drugs work, because the future rests on whether we can resolve that question. If we can understand how they work, knowledge will move in two directions, in one direction it will tell us more about the key facets underlying a disorder. That was the great hope. And in the other it'll allow us to use this behavioral compartmental model that's been available for ten or twenty years, to target transmitter systems. As we'll be able to do that more efficiently and more successfully, we'll be able to manipulate behavior much more easily. I do want to say something about one of the disappointments of the last thirty years and that is about the "bad" drugs, the LSD-type drugs I spoke of in the beginning. . Those who remember that era, recall what a wild era it was. From the standpoint of NIMH, we used to have people come to see us, perfectly sound, established investigators, who

had ideas of putting these drugs into the water of Jack Kennedy and Kruschev to bring peace in the future and so forth. They had seen the light. Of course we worked with these people, because there had been wild ideas before and some worked. But this movement frightened the field and, in the course of it, we left these drugs rather early. There's not much we could have done about that, because they were potentially very harmful. But anyone who saw the impact these drugs had on the mind, from a psychological point of view, had to feel we were knocking on the door of a better understanding of what goes on in the brain. These drugs produced remarkable changes in ideas, perceptions, and images, given in a dosage almost invisible to the naked eye. Yet, somehow, we couldn't quite get a grasp on them that would allow us to learn enough to move on in a way that would have an effect on science. We watched the drugs get buried under an avalanche of bad publicity and bad effects. Not that we could afford to let their indiscriminate use go on, knowing how much damage they can bring about. But drugs that have that kind of power should not have been abandoned. I'd say that is another lost venture.

JE: A kind of a missed opportunity.

MK: We have, in some way to be able to open that door again, without losing control of the potentially harmful things associated with it.

JE: Were there other points you wanted to make about the history and your role?

MK: I'd just like to say that I consider myself very lucky that through a fortuitous set of events I wound up in that job at the PSC at such a young age and got to see so much of what was going on in the country and the world. I was in a favored position for many years to watch this whole field of neuropsychopharmacology develop. When I left after a span of time in psychopharmacology and clinical research, I became a Professor at Albert Einstein College of Medicine for ten years. I tried to develop a new program in psychology that would take advantage of the different ideas from the different disciplines I came across. But this is an era in which everything seems to be more constrained, pulling back, so we've got to be patient and maybe it will open up again at some point. That's the story.

JE: Thank you.

DONALD F. KLEIN

Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 13, 1994

LH: I am Leo Hollister and I am interviewing Donald Klein.* He has been president of this great organization and he's been Mr. Panic Disorder for the last 30 years. In fact, I'm normally against new diseases, syndromes and signs, but if somebody came up with the idea of a Klein Syndrome for Panic, I would be perfectly agreeable to it. But, how did this all get started, Don? What made you go into medicine, in general, and psychiatry, in particular?

DK: I wanted to be a scientist since childhood. No one in my family but my father fostered this by regular trips to the museum of Natural History and Planetarium. Actually, when I was in high school at the Bronx High School of Science, a great experience, I wanted to go into Chemistry as a research scientist. I had been fooling with chemistry sets since I was a kid. I loved it and did well in Chemistry. And, then, when I got to college, I stumbled onto Freud. I got to college young; about 15 when I started. And I was wandering around the stacks of books in the library one day and found Freud's books; he was talking about all the things I was interested in. It was mostly sex and I figured this guy must have something going for him. So, I really got interested and read a great deal of what he wrote; my desire at the time was to be a research psychoanalyst. And I understood that to be a psychoanalyst you have to be an MD. It struck me that was pretty foolish, but I didn't mind becoming an MD.

LH: So, you choose to become a psychiatrist before you actually entered medical school. You were going into psychiatry to be an analyst.

DK: Exactly, psychiatry was sort of a steppingstone to become an analyst. Anyway, in 1948 I graduated from college, top of my class. I was 18. I couldn't get into medical school, probably because the Vets had all come back then, but also anti-Semitism for medical school admission was very real. So, I spent a year in NYU graduate school in Biochemistry and Physiology, which was not a lost year as I learned how to use a library and some fundamentals of physiology and endocrinology. Finally I got admitted to Long Island College of Medicine (LICM.) The only other acceptance was from Howard. LICM was extremely clinical, generally considered a 'baby catching' trainee school. However, the clinicians were astute and critical, and the training to deal with

* Donald F. Klein was born in New York City, New York in 1928.

patients has stood me in very good stead. In my senior year it became Downstate University. Downstate made a budding hematologist out of me, because psychiatry was so lousy and hematology, as taught by Janet Watson, was really engaging. She was a pioneer in hemoglobin molecular structure and Sickle Cell anemia. I worked as a laboratory assistant to Norman Kretchmer who had his PhD and was in my MD class. We did paper chromatography when there were only two papers, winging it with Pyrex pie-plates. Norm went on to be the head of NICHD and remained a good friend, although he consistently referred to me as a "spook". The psychoanalysts were terrible; they spent all their time reading to us from their textbooks, although we all knew how to read, and telling us if we had a question about anything that was our resistance or counter-transference. But, it didn't turn me off completely. Anyway, I interned in the Public Health Service. It was in the Korean War and I hoped to spend two more years with the Public Health Service, taking care of tubercular Eskimos, rather than go to Korea. But I got fired at the end of my intern year, because Eisenhower had a reduction in force and the bottom half of the intern class was dropped. I was squarely in the bottom half, because I didn't get along with them very well at all. I asked too many questions. However, their psychiatry rotation was mentored by two very bright psychoanalysts, Richard Silberstein and Milton Horowitz, who also thought questions were resistance, but were personally engaging and intellectually alive. This revived my psychoanalytic interests and I re-developed the misguided goal of being a research psychoanalyst. So, I was scurrying around. I had a wife and a kid at the time, and felt lucky when I got a job as a first year resident at the Creedmoor State Hospital, where they gave me a house and a gardener, a maid and, probably, a chauffeur.

LH: Who was in charge of psychiatry there at the time?

DK: Nobody. When I was a first year resident, in 1953. Creedmoor was a 6,000-bed locked hospital and after I was given a book on the mental status, I was told that I should take care of my 300 patients upstairs. They also told me that the nurses would teach me how to do ECT but fortunately I knew that from my internship. That was all the training I got. It was a great experience, but also a great responsibility. The patients were fantastic. We had no psychotropic drugs at all in 1953, except paraldehyde and amytal; all we had was ECT and nursing care. And then, primarily because the draft was after me, I went back into the Public Health Service and spent two years at the Narcotic Hospital in Lexington, KY. That was a wonderful experience; that's what's turned me onto Psychopharmacology.

LH: Now, you jumped out of the Public Health Service earlier, but, then, you went back into it?

DK: I called them up and I said, "Look, I've got a whole year of psychiatric residency, don't you need me?" And, they said, certainly, with a whole year of psychiatric residency, my goodness we certainly need you down in Lexington, KY to run the Admission and Withdrawal Service. I didn't know much about admission or withdrawal or narcotic addictions or anything at the time, but I went there and the guy in charge took me on rounds once. And from the next day I was on my own. I had 70 beds to take care of using methadone withdrawal. It was a terrific place and I liked it a great deal. I had complete misconceptions about what addiction and addicts were like.

LH: There were some giants working there at the time.

DK: Well, Abe Wikler who was probably the smartest guy I ever met, thinking deeply about psychiatry and pharmacology. He wrote a book called The Relationship of Pharmacology to Psychiatry. During the period I was down there, I had the opportunity to discuss with him what the contents of the book and its layout should be.

LH: It's a classic text.

DK: A classic book, which fell like a lead balloon, because it just came out after imipramine was introduced, so it had nothing about the antidepressants. And he missed the boat on lithium. He felt that lithium was having its' effects by toxicity. Yet because of his thinking and the discussion of how you go about studying drugs and relating them to psychiatry, the book may still be the best single volume in the field. The book disappeared, so I don't know anybody who knows about it any more.

LH: Heavily underused, right?

DK: I tell people about it, especially my juniors. Anyway, I got involved in Lexington with studies on reserpine, chlorpromazine, and LSD for a two-year period. The LSD studies were being financed by a mysterious foundation. As we found out later, they were funded, by the CIA. The criteria for selecting subjects and the requirements for inclusion in the LSD studies were pretty clear. The people selected were from those with two, five-year federal prison terms, who considered themselves "stoned junkies" and were never going to recover.

LH: A CIA front?

DK: The whole thing was due to brainwashing concerns, which was the glib explanation of the time. The Koreans had American pilots, who had been shot down, on TV saying they were capitalist stooges. You didn't see the rifle pointing at them off screen, so it was assumed they had

been brainwashed and LSD was the obvious culprit. Anyway, I made good friends with Wikler at that time although he was really put off when he understood I wanted to be a psychoanalyst. He thought that was not too smart.

LH: Heresy.

DK: But Lexington was actually an analytic hospital. It was run just like Chestnut Lodge. The head of the hospital was a training analyst and 50 patients were in intensive psychotherapy. They had a psychotherapist and an administrative therapist, who took care of all the grimy details, like parole. In retrospect, it was a completely bizarre setting. I remember seeing at least one authentic miracle. I was in charge of a ward with 100 veterans who had been hospitalized continuously since World War I. They weren't in the VA, because there wasn't any VA for World War I veterans. They were under a thing called Executive Order, and got to Lexington from the psychiatric unit at St. Elizabeths Hospital.

LH: But weren't they drug-users?

DK: No, they were just plain army folks, who had gone psychotic during or just following World War I. Most of them sat around on benches and looked at the wall. They had excellent nursing care and did all sorts of interesting things with occupational therapy and psychotherapy. But whatever they got had not done any good to anyone. So, I decided to give them all Thorazine (chlorpromazine), 200 milligrams a day, which was a big dose then. One of them came up to me, after about six weeks, and said, hey, Doc, when am I getting out of here? I never thought that could happen. It was really remarkable and made a big impression. I left shortly after and went back to Creedmoor, finished my residency and got into research. I was working first with a group of psychoanalysts, who were running an intensive psychoanalytic clinic devoted to six families with autistic children. These identical autistic twins walked around on their toes. I asked the supervising psychoanalyst how the mother had done that, but was told this was resistance. That was somewhat disillusioning. When that boondoggle shut down I worked for John Whittier who was unusual, an MD, PhD, psychoanalyst and veterinarian. We did one of the first controlled studies on mepazine, a drug that everyone said was terrific because it didn't cause those terrible side effects and mental confusion like other phenothiazines. The only trouble was that it didn't work. It was the only phenothiazine taken off the market. That experience reaffirmed that double blind, randomized, controlled studies were a pretty good thing to do. I went to the New York Psychoanalytic Institute about 1957, and that's a long sad story, in itself. Essentially, I burned out two analysts and they got rid of me. I ended up in 1959 at

Hillside, working for Max Fink. Hillside was a psychoanalytic hospital but Max Fink was a whole different character. He was a neurologist and psychiatrist who had psychoanalytic training and worked with Morris Bender. He was studying ECT and used it as an experimental treatment to be studied for its effects on brain function, rather than just as some sort of punishment. Also, he wanted to get involved in studying the new psychotropic drugs. And that's how I got going. Max was a complete nihilist. He did not believe in diagnosis. He thought there was no evidence for any of the diagnoses because people in reliability studies, making independent diagnoses, did a very bad job of it.

LH: Still do.

DK: Probably. At least we have some inclusion/exclusion criteria now, but then we didn't have anything. So to study the new drugs Max and I went to the head of the hospital, Lew Robbins who was an analyst, but very broadminded. He wanted to understand things. We said we've got to collect data on what these drugs do to people, and Lew agreed we should do it so I was the only person in the hospital who could write orders for medication. I would write orders for anybody but the residents had to first call me up so I was able to ask why they were putting the patient on medication. I also interviewed the ward staff, resident and supervisor as well as the patient. Then I would see the patients every week until they were discharged. Anytime the residents wanted to change the dose or the drug, they had to call me up and tell me why. That was the best learning experience I ever had, because I saw all sorts of things done that I never would have done, and some worked and vice versa. I did that for almost two years. During that period, I evolved this notion of pharmacological dissection. The idea came from an observation that there were distinct patterns of response to Tofranil (imipramine) and Thorazine (chlorpromazine). One of the patterns I came upon early was that there were patients who had what we now call panic disorder with agoraphobia. In those days, they called them schizophrenic although not delusional or hallucinated. But when patients with this pattern went on Thorazine, which we thought was an anti-anxiety drug, they got much worse. That was very disappointing because at the time Menninger believed that anxiety caused everything. Thorazine was good for schizophrenia which goes with very bad anxiety, so it should have been good for lesser anxieties. But it wasn't. When we got them, as a last resort, on Tofranil, it stopped their spontaneous panic attacks. I published that in the early 1960s but nobody believed it. They thought it was just some sort of crazy idea. First of all Tofranil was an antidepressant and these people weren't depressed.

And, besides, Thorazine was an anti-anxiety drug, so why did it not work? It struck everyone as very strange you would have an antidepressant drug knock out panic, the worst form of anxiety, and make it possible for patients who were afraid to leave a room, go out by themselves. I did a long series of double blind placebo controlled studies which showed I was right. Imipramine stopped the panic attack and I developed a theory that agoraphobia was secondary to panic inciting anticipatory anxiety, followed by avoiding situations where you might get a panic attack and couldn't get help or get out.

LH: Did you try any MAO inhibitors at that time?

DK: Yes, I did. As a matter of fact, in our second paper we reported on 4 patients, who responded positively with MAO inhibitors. But, I was able to point out that what we had wasn't a general antidepressant effect. These patients responded badly to ECT. So it wasn't that they were just depressed in some peculiar way. For many years it was thought that all the antidepressants worked to block panic. Now we know there are antidepressants that don't work. I came up with this idea of pharmacological dissection, putting people together with a similar pattern of response to medication to see if there was something in their baseline state you could use diagnostically. That's the way I've been thinking about refining diagnosis.

LH: It is a rather unusual way of making a diagnosis; choosing a drug that you think is good for that diagnosis. You would make the diagnosis after the fact?

DK: Exactly. The first big study we did in this area of research is still one of the biggest studies done in a single place. We took 300 patients and randomly assigned them to placebo, Thorazine or imipramine and tried to figure out what they responded to. That took me out of my antidiagnostic phase, because the best way I could make sense of the various drug response patterns was to recognize there were relevant diagnoses. But they weren't the diagnoses like schizophrenia that everyone was using loosely. They had been described a long time ago as agoraphobics and even before that as secondary to panic attacks by Freud. But there were depressed people, who responded poorly to imipramine and I recognized those were the ones the English described as atypical depressions.

LH: That was Will Sargent?

DK: Sargent, Dally, West, and a whole group of English psychiatrists, who were very good observers, and recognized these peculiar depressions, which did not respond to ECT and tricyclic antidepressants but to monoamine oxidase inhibitors. I followed that up, years later, with

Fred Quitkin, when I got to Columbia in 1976. It became the largest series of randomized placebo-controlled trials contrasting imipramine, phenelzine and placebo. Phenelzine worked by far the best. In the new DSM-IV, atypical depression is included as a parenthetical modifier.

LH: In those days, you were trying barbiturates first in the treatment of panic on the assumption those were considered antianxiety drugs, but these patients didn't respond to barbiturates. Is that correct?

DK: Panic wouldn't respond, but between panic attacks on barbiturates they would feel better. But, then, a panic attack would come along and they'd start taking more barbiturates. They thought a panic attack was the outgrowth of their chronic anticipatory anxiety. If anything, it was the other way around; it was the panic attack that was promoting the chronic anxiety. So, a fair number of people who had a panic disorder ended up getting hooked on barbiturates and alcohol, which helped anticipatory anxiety but not panic attacks.

LH: In the 1980's alprazolam came along and that seemed also to work in panic.

DK: There's no question that alprazolam works in panic. What I said was panic had to differ from anxiety because imipramine treated the panic and the person was left with chronic anxiety and phobic avoidance. I didn't say, although a lot of people thought I did, that generalized anxiety disorder would not respond to imipramine. I simply said that chronic anxiety would take a long time to go away. We then showed that for people who only had specific phobia and anticipatory anxiety, but not agoraphobia, imipramine was no better than placebo. Now, the question was whether imipramine works in panic disorder and alprazolam in generalized anxiety disorder? The answer seems to be that imipramine and alprazolam work in both. So that does confuse the issues, in terms of trying to get a neat dissection. There were some interesting findings regarding this in the Upjohn study when they compared impramine and alprazolam. Two British psychiatrists did a cluster analysis of the patients' description of their panic attacks, and found that for those patients who had a lot of dyspnea, shortness of breath, imipramine worked better than alprazolam, but for those who didn't have a lot of shortness of breath alprazolam worked better than imipramine. So, it struck me that maybe there are different sorts of panic attacks. That is another type of pharmacological dissection. In generalized anxiety disorder, it takes 4 to 6 weeks for imipramine to work, and it works in doses of 80 or 90 mgs a day which aren't good enough for panic disorder; patients with panic disorders need more than that. It's still not clear to me whether the very high potency benzodiazepines,

such as alprazolam, clonazepam and bromazepam, which are effective in panic disorders, are doing something different than the lower potency benzodiazepines. There's only one study on diazepam in panic disorder, but in that study they ran the dose up to about 45 milligrams a day .The patients got somewhat better, but the panic measures were quite unclear. So, I think it's still moot.

LH: 40 milligrams of diazepam would get you in the ballpark, on the basis of the comparative potency of diazepam and alprazolam.

DK: That's true.

LH: So pharmacological dissection in psychopathology led to a new formulation for panic attack?

DK: Yes. And, then, when I got to Columbia, we started studying the psychophysiology of panic attacks. Back in the 1960s Pete Pitts discovered giving intravenous lactate to patients he called anxiety neurosis created a panic attack. But he got into a fight because it was argued that the tremor and feeling of paresthesias the patients got from lactate frightened them into a panic attack. It was argued non-specific stress produced the panic. What Pitts then did was to give the patients EDTA, a powerful calcium-chelating agent, which threw some into tetany but the patients didn't panic. But that got ignored and the general consensus was that lactate was doing nothing specific. Then, an English psychiatrist, Desmond Kelly reported on 8 agoraphobics who panicked after lactate and, when he gave an MAO inhibitor to these patients, 5 out of the 8 got better. Then he gave lactate again and the 5 patients, who had gotten better on the MAO inhibitor, didn't panic anymore. I said that's more than conditioning so, when I got to Columbia, I set up an experiment with lactate and imipramine, showing that imipramine blocked the panic and even after the patients were taken off imipramine for a month they did not get panic if you gave them lactate again.

LH: It's kind of desensitization.

DK: It pushed the switches around. I wasn't sure how, because we brought back a number of them six months later. They were panic free for six months and they had not expected to get again a panic attack at all. But what we found was that about 40 percent of them panicked. Whatever impramine does, I think it down regulates the suffocation alarm, goes away eventually.

LH: How did you get to this "suffocation alarm" hypothesis?

DK: First of all, everyone assumed that panic is a sort of fear, which makes sense. But it doesn't look like fear, because the outstanding feature of the panic attack is dyspnea that, depending on the seriousness of the attack, occurs in 70 to 90 percent of patients. The person says I can't

get a deep breath; I'll run to the window; I'll throw it open; I just can't get a deep breath. And, that's not part of fear. There have been seven good studies of people who have been shot at in combat or jumping out of airplanes and they all report palpitations, trembling and sweating, but they don't report dyspnea. The other thing that tipped us off that panic wasn't fear was that when we took the blood levels of epinephrine, norepinephrine, cortisol, and ACTH, of panicking patients it was flat. There was no surge of these substances in panic attacks as you have with fear. So we reported that lactate was suppressing the hypothalamic pituitary adrenal system, but got the same effects with inhaled carbon dioxide, which doesn't give you an osmotic load. Scott Woods, at Yale, took patients, wired them up, put cannulas in, walked them into situations where they were likely get a panic attack, like a supermarket, and again found no cortisol surge during clinical panic. Then I started to think isn't it peculiar that the two powerful panicogens which don't produce any increase in cortisol are lactate and carbon dioxide, substances which are intimately tied in with what happens to you if your respiration is compromised. The surest sign that you're not breathing enough is that your blood carbon dioxide is going up. And lactate is a remarkable substance that only comes from one place and it only goes to one place. When glucose is being burned, it goes through pyruvate on its' way out as carbon dioxide but if you don't have enough oxygen it gets shunted into lactate. So you have two sure signs there that there's something wrong with your respiration: carbon dioxide or lactate going up. And those two things induce panic. So, that's what got us to develop the idea of a suffocation alarm system. We've been pursuing that idea, and written about it extensively. We've got a lot of good circumstantial evidence that situations where carbon dioxide is likely to increase are those where the amount of panic increases. When carbon dioxide is low, or kept low, panic is unlikely to happen. Childbirth is a situation which, according to all the psychological theories, should be very panicogenic. There are many internal sensations signaling danger. You are actually in danger. There is uncertainty, because you don't know what's going to happen next. In fact, patients with panic disorder never panic during childbirth, perhaps because people have the lowest blood carbon dioxide levels during childbirth.

LH: Because they are hyperventilating?

DK: Hyperventilating at a furious rate. I want to tell you one more story. If this works out, I will be very pleased. What an experimenter ought to do when he or she develops a theory is to look for a place where the theory doesn't stand up, because that's a way to enrich the theory. So my

theory implies that anytime somebody is suffocating, asphyxiating, they ought to panic. And, in general, that's true, but there's one big exception, which nobody had ever pointed out and this is carbon monoxide intoxication. When people asphyxiate with carbon monoxide, they just fade away. If brought back before they die, they don't tell you that they had a panic reaction. People have been found in their cars in the garage but nobody runs out of the garage, panicking. So, that seems to be a hole in the theory.

LH: Carbon monoxide intoxication would be primarily oxygen deprivation.

DK: The carotid body is measuring both oxygen and carbon dioxide levels and if the oxygen level goes down, or the carbon dioxide level goes up, that stimulates the brain respiratory centers by the 9th and 10th nerve. So the carotid body is a suffocation monitor. Sol Snyder found that carbon monoxide was a neurotransmitter, so maybe it's screwing up the alarm system. Then I got a letter from Sol, saying they have shown that carbon monoxide is an inhibitory neurotransmitter in the carotid body. It gave me an idea for a terrific study which I was trying, unsuccessfully, to get through the IRB. The idea was to produce panic attacks with 7 percent carbon dioxide in panic patients and by mixing small amounts of carbon monoxide with carbon dioxide, the alarm system should be sabotaged and stop them from panicking. I think this would really be conclusive evidence for the theory. So I thought we'll find out, but never did.

LH: It would be an important study. It's very interesting you mentioned that shortness of breath signifies panic. I remember talking with Mandel Cohen a few years back and we recognized that some of the patients, who had nocturnal panic attacks, would wake up in the middle of the night, gasping for breath and fool you. Of course, they didn't have a large heart or wet lungs so that is an aspect of fear and anxiety.

DK: Mandel Cohen was 40 years ahead of everybody. He showed that carbon dioxide was a panicogen, but nobody picked up on it. He went to World War II veterans and showed that they did not have dyspnea when they had fear on the battlefield. He said back in the 1950s, that whatever the peculiar thing was that happened in "neurocirculatory asthenia" it was not fear. He was very clear about that. We invited him to give a lecture at Columbia where he did not endear himself by comparing the influx of European analysts to a swarm of locusts! He was a real pioneer.

LH: He certainly was. From now on I suppose you are going to develop and test this hypothesis in every way you can think of.

DK: Right. We have another hypothesis we're working on. We pointed out a long time ago that half the patients with panic disorder have a history of separation anxiety as kids; they remember they didn't want to go to camp; they fought going to school; they stayed out of school; they wouldn't go to sleepovers. With my wife, Rachel Klein, we have done a 20 year follow up on school phobic kids we treated, and the only thing that developed, in excess, was panic disorder in later life. So how do you bring together the two hypotheses, suffocation alarm and separation anxiety? Well, it has been shown in animals that endorphins decrease both separation anxiety and carbon dioxide sensitivity. So it's conceivable there is some link there. If you had a situation like periodic endorphinergic deficit, that in my opinion, would increase both separation anxiety and suffocation sensitivity.

LH: Has anybody ever looked at submarine crews? You have a situation where people are threatened with suffocation or drowning.

DK: I went back to the work by Haldane, done in 1918, on submarine crews. What came out of that study is that carbon dioxide levels in subs are 2% and you can become a submariner only if you can adjust to that. We're trying to experiment on the endorphin line and find out if you give lactate to normal subjects what happens. We already know that if you give naloxone to normals, very little happens. Pickar gave a whacking dose of naloxone to normals and they got nervous and anxious, but that was about it, nothing terrible happened. But I wonder what would happen if you gave lactate to subjects pretreated with naloxone, whether normal subjects given an endorphinergic deficit are lactate sensitive. We'll see how that works out.

LH: I don't recall anybody placed on naltrexone develop panic.

DK: No, there is no report on any patient who developed panic after being put on naltrexone. There are reports on some peculiar episodic dysphorias with naltrexone but they are not well documented.

LH: If you muck up a system as important as the endorphinergic system, it is likely something will happen. We reported a number of years ago dysphoria produced by naltrexone that would probably explain why it's so hard to get it accepted into clinical practice. People don't feel particularly good on it. Well, you've made a career of pharmacological dissection and developing a systematic description of agoraphobia and testing its' pathophysiology. It will keep you busy for awhile.

DK: I hope so.

LH: Since 1976 your career has been at New York Psychiatric Institute.

DK: Right. I'm Director of Research at the Psychiatric Institute, which is a nominal title. I don't have any real power, it's just one of those titles.

I do have a very big department in Therapeutics that has an anxiety clinic, a depression service, a family study group, and a biological studies group. They do a lot of work.

LH: That has been very productive in terms of publications. Well, that's an interesting career you've had and more to come, I think.

DK: I certainly hope so. It was also fun being involved with ACNP; it's a very elite organization. People, who are in it, are very smart successful people. One of the problems with being successful is that it makes you somewhat conservative, so you don't want to rock the boat too much, because, after all, you've done all right. But there have been a number of developments recently that should shake us up in terms of how psychopharmacology research is going in coming years, both from the point of federal support and from the pharmaceutical industry. The ACNP could play some proactive roles there. I hope it will do.

LH: You've been a creative thinker in this line; what do you think the ACNP should do?

DK: The ACNP ought to try to formulize a relationship with the heads of the federal agencies, including the FDA, NIH and so forth, and meet with them regarding their agendas. For instance, I'm head of a mental health clinical research center but I'm not at all certain whether mental health clinical research centers are viewed as a sensible way to spend money. I think psychiatry is in a relatively primitive state compared to internal medicine. They're way ahead of us in objective measurements and physiological understanding. Are RO1s by independent investigators a really good way of funding research?

LH: That's Rosalyn Yalow's idea. You provide support to individuals rather than huge amounts of money to centers.

DK: For Rosalyn that makes great sense, but for psychiatry, we still need to get critical masses that can collaborate as experts in a variety of fields, because we're nowhere near Rosalyn Yalow. For that reason centers make sense in psychiatry. It would be interesting to have a discussion about that with someone like Dr. Harold Varmus.

LH: What do you think of the future of psychiatry, with everybody nipping at our heels and trying to get a piece of the turf? You know psychologists will soon prescribe drugs.

DK: I'd be surprised frankly if that happens in the near future, because they're not qualified; they don't have any knowledge of medicine and drug interactions. The training they get doesn't qualify them for it and malpractice lawyers would have a field day. So I don't think that's going to happen. But the psychotherapy area will change. Psychiatrists who solely practice psychotherapy, will be people dedicated to surviving on

low incomes, because the psychologists will undercut the psychiatrists, and the social workers will undercut the psychologists, and the psychiatric nurses will undercut the social workers. You won't be able to make a living doing solely psychotherapy as an M.D. Psychotherapy has a place in treatment but it's a function that can be delegated, so it ought to be supervised, following proper diagnosis. In my own practice we have psychotherapists, but they don't work up the patient. The psychiatrist does that and dispenses the medication. Psychiatrists collaborate with them and do whatever else is needed; internal medicine with a psychosocial backup. It makes sense to me.

LH: Undoubtedly, there's going to be some big changes in the not too distant future.

DK: Right.

LH: I'm sure you'll be part of the thinking about it. You have always applied your agile mind to many issues and I look forward to seeing what you do in the future.

DK: Thank you, Leo. I appreciate it.

JAMES C. KLETT

Interviewed by Leo E. Hollister
Washington, DC, April 12, 1997

LH: We're in Washington to continue the series of interviews on the history of psychopharmacology sponsored by the ACNP. I'm Leo Hollister and my guest today is Jim Klett.* Jim is an old friend, colleague and co-author. Jim, you're still out in Maryland?

JK: Bel Air, Maryland.

LH: That's a wonderful spot. Tell me, how did you get started in your career?

JK: I did my undergraduate work at a small Liberal Arts College in Jamestown, North Dakota where I was born and raised. I intended to major in mathematics but as sometimes happens, I encountered an inspirational teacher who captured my imagination. So I ended up with a major in psychology and went on to graduate school, first at Washington State College in Pullman, then to the University of Washington in Seattle. I was majoring in clinical psychology, but still felt attracted to mathematics. I had some good teachers at both schools. At the University of Washington, there were two very well known quantitative psychologists; Allen Edwards, who wrote many of the statistics text books of the day, and Paul Horst, who was one of the founders of the Psychometric Society and editor of Psychometrica for many years. Those two people contributed to my continued interest in statistics, but I had committed myself to a career in clinical psychology by that time. The Veterans Administration (VA) had an early involvement in controlled clinical trials with a study of prefrontal lobotomy in six VA hospitals, and as a VA trainee in clinical psychology, I ended up doing some of my early work testing these patients, before and after their surgery. That was my first taste of clinical trials.

LH: No wonder you dropped out of clinical psychology after dealing with prefrontal lobotomy.

JK: Right. Cecil Peck, who was Chief Psychologist in the VA central office (VACO) at that time, knew I had a research interest, so my first job was at a VA Hospital in Northampton, Massachusetts. This had been one of the hospitals that participated in the lobotomy trial, but also there was an interest in doing some early psychopharmacologic research. I spent a couple of years partially involved in the ongoing lobotomy study. Finally, I was recruited for the staff of the Central NP Research

* James C. Klett was born in Jamestown, Dakota in 1926.

Laboratory (CNPRL) at Perry Point by Ivan Bennett, who was at that time in VACO, before he went off to Eli Lilly, never to be heard from again. My initial assignment was to help write up the results of the lobotomy study. The Cooperative Studies of Chemotherapy in Psychiatry were just starting. Incidentally, the VA was also involved in multi-center studies of chemotherapy in tuberculosis.

LH: Really, the Armed Forces and the VA? That was in the 1940's.

JK: Yes. I was making the point the VA had a considerable involvement in large-scale multi-center clinical trials, and was organizing the first cooperative study of chemotherapy in psychiatry at the time I came to Perry Point. There were some very good investigators, like you, doing single investigator studies at that time. So there was quite a culture of research in the VA when I joined. Of course, I stayed at Perry Point for the next 35 years or so.

LH: It's not a bad place to be.

JK: I was attracted to it because my main interest was in statistics and clinical trials methodology, and here was a program in which we could have large patient samples and do definitive work on comparisons of treatments. That added up to be a very satisfactory career from my point of view. Another aspect was the many people with whom I was able to collaborate over the years, people whom I admired a great deal through our cooperative studies program. We had an Executive Committee, of which you were a member for many years, and we had a lot of very fine people from within and outside the VA who served as members. I don't see the VA as currently playing as prominent a role in neuropsychopharmacology as they did at that time. There are some excellent investigators here and there, but it doesn't seem to be a coordinated effort as it was in those days.

LH: The VA is being swept up in this revolution of medical care delivery and nobody knows what their fate is going to be, especially as the large echelon of World War II veterans dies off. What are we going to do with all these magnificent hospitals?

JK: We need to pay some attention or respect to the people who played a role in the early days. I mentioned Ivan Bennett. He brought a lot of energy to that job before he joined Lilly. Clyde Lindley, whose name you might not find in a computer search of the psychopharmacology literature, was the sparkplug who helped to organize and keep going this program of multi-centered trials in psychiatry.

LH: Clyde had a wonderful knack of being able to get people to work together, it was his specialty. He took some psychology but he never got an advanced degree; his specialty was personnel management and

he did an admirable job. So, you were pulled in just as the VA cooperative studies were getting under way.

JK: The first multi-center study had passed the planning stages and was distributing the blinded drugs. Perhaps I should give a capsule history of the CNPRL. At this time, there wasn't a separate Research Service in VACO. There was a small group within the Psychiatric Service; Richard Jenkins, a psychiatrist, Quinter Holsopple and Maurice Lorr, both psychologists, who had been involved in design and coordination of the multi-site study of prefrontal lobotomy. Lorr was well known in neuropsychopharmacology circles for the development of some of the rating scales we used for many years.

LH: The IMPS, was the standard scale.

JK: The Multi-dimensional Scale for Rating Psychiatric Patients (MSRPP) was the earlier one. Later on, several of us (Jack Lasky, Doug McNair and I) collaborated with Lorr on the development of the IMPS. In any event, Quinter convinced VACO to open a laboratory at VAH Perry Point to have access to patients for pilot testing and develop rating scales. He wanted to get out of DC and to Perry Point, which, as you say, was a nice place to live. He was joined by Mordecai Gordon, another psychologist. That was the nucleus but Quinter died and they recruited Jack Lasky to replace him as Chief of the Center. Jack and I arrived at about the same time.

LH: I wonder what happened to those people. I haven't heard about Lasky.

JK: Maury Gordon left the VA and went over to the National Institutes of Health.

LH: He was on some neonatal study there.

JK: Right. I used to run into him occasionally before his death.

LH: And Jack?

JK: During the Kennedy years, Jack was seduced by his old professor from Michigan to help run the Peace Corps. He left me as Acting Chief of the CNPRL and after leaving the Peace Corps, rather than come back and displace me, he was good enough to go to the National Institutes of Health. Jack was always a good guy.

LH: He became a Study Section Chairman.

JK: Executive Secretary.

LH: But, that was the last I heard of him.

JK: Well, he stayed there until retirement some 10 or 12 years ago, and he's now up in New England. He taught at a small college for many years after he retired. At CNPRL our staff included such distinguished colleagues as John Overall, who one would have no trouble at all identifying by a computer search.

LH: John's been very active, and right now we're colleagues again. He was the main reason I went from California to Texas. Maury Lorr got lost in the shuffle after John and Don Gorham came up with the Brief Psychiatric Rating Scale; a very useful instrument, wasn't it?

JK: I found it to be so. But, I could also understand why in the competition among scales that the Overall Gorham BPRS won out, because it was a brief scale.

LH: It wasn't as atomistic as the LORR scale.

JK: That's right, and that was an issue where one could argue whether it would be best to have longer scales with redundancy or brief judgmental scales. What happened is the BPRS is still in wide use but the MSRPP and the IMPS are rarely used any more.

LH: You and Maury did a lot of early work on identifying the factors.

JK: Maury became Chief of the Outpatient Psychiatry Research in VACO while the CNPRL focused on inpatient research, but Maury and I collaborated a lot and we were interested in the typology of psychosis for a while. That had been a long interest of Maury's and we wrote a couple of books on typologies. I finally lost interest in it, but Maury has pursued it. Gil Honigfeld spent about five years with us before he went off and reemerged at Sandoz.

LH: As the developer of clozapine.

JK: As the Project Leader for the clozapine research, but he did his internship at Perry Point.

LH: I don't know what his reaction might have been when they told him, "Take this drug and see what you can do with it," because it didn't look very promising at first, but Gil saw it through.

JK: I agree.

LH: Now clozapine is considered to be the most revolutionary development in antipsychotic drugs in the last twenty years. There were a lot of interesting people then. You were one of the co-authors of the very first report on Project #1.

JK: No, that's not the case. I think there were six authors including Maury Gordon, Dr. Frank Casey, the Director of the Psychiatry Service in VACO and I believe you were also an author.

LH: Yes.

JK: I wasn't involved; I came in on the second or third major study. Another person I'd like to mention with special emphasis is Gene Caffey. I've always collaborated as a member of a team, and for many years I worked with Gene Caffey. Caffey was a member of the Executive Committee. He was also the Chief of Staff at the VA Hospital at Perry Point, so it was

convenient to work with him, but he's also one of the most congenial people I've ever known.

LH: Gene was a wise old hand; he didn't say a whole lot, but when he did it meant something. Those were exciting days, the VA studies preceded ones that occurred in several state systems, one in California, another in Delaware with Fritz Freyhan and a few scattered around the country. It also preceded the study of the Psychopharmacology Service Center.

JK: Right. There's another study that occurred about that same time by Al Kurland and Tom Hanlon at Spring Grove and was a large study comparable to our Project #1 or #2.

LH: Did that precede or follow?

JK: It was done at about the same time. But the ones done at the NIMH got all the attention, for obvious reasons. The VA wasn't getting enough money and NIMH had a much better PR system than we did.

LH: That study has been misinterpreted because it's alleged it shows a placebo effect in schizophrenia but if you look carefully there were as many people who got worse as got better on placebo, and secondly, diagnosis in those days was not very good. They probably had a lot of hypomanics and manics who spontaneously remitted, but in any case it got the publicity. I don't understand why because the VA studies were published in good journals.

JK: That reminds me of another thing. In those days there wasn't a single book on how to do a controlled or a multi-center trial. Now you could have a five-foot shelf of books on how to do them.

LH: You were the co-author of one of the first.

JK: Another figure who was very helpful at that time in that context was Tom Andrews, the Chairman of the Psychology Department at the University of Maryland, who participated in the development of that first protocol.

LH: He was the prime mover as far as statistics were concerned.

JK: Yes, he and Maury Gordon. So it was very helpful to have Tom Andrews available; he was in his 40's, when he died.

LH: I think so, very early.

JK: He played an important role. I can only think of one professional statistician active in the field at that time and that was Sam Greenhouse, who by the way has a son by the name of Joel Greenhouse, who's also a statistician, a very nice fellow. That particular function was filled by quantitatively trained psychologists, like John, my-self, Doug McNair and a few others, and it was almost always characterized by collaboration between a psychiatrist and a quantitatively trained psychologist. That was a very productive kind of arrangement. Now, of course, we've moved into a different era. There are still a lot of good psychologists

around that I used to run into in my site visiting, but we now also have a lot of very good statistically trained people, like Phil Lavori and others that are active in the field.

LH: Now back in those days how to handle all those data fields was not clear.

JK: Right. These were early days for computers and data processing.

LH: You were using punch cards in those days?

JK: Yes, and now many people don't know what an IBM punch card looks like. But, we had made arrangements with the statisticians at the Bureau of Standards to analyze the data from that first study. They didn't have canned programs to do it. They had to write the programs to do the multiple co-variance analysis. And it took months to get the program ready, so much so that we were worried it might hold us up. In those days we would take a couple of boxes of IBM cards, drive to Washington and leave them with somebody, and come back the next day or a week later to pick up the results.

LH: Bring out a box of punch cards?

JK: Right, it was a whole different era.

LH: Now, I suppose every pharmaceutical company has in-house statisticians who design protocols. In fact, the fun has gone out of it. They write the protocol and you give them the data and they analyze it and you never see it. They hire some flack to write up the results. It's not the way it used to be.

JK: Sad but true. It was better when we had control of the process.

LH: In those days there was still dispute as to which way to handle the data, and exploiting more sophisticated statistical techniques than usual.

JK: I thought of something that is amusing. In our trials, to provide for a double blind control, one company like SKF would provide their drug and another company would provide theirs. We would specify they had to be in a canister, so that would be standard. When the drugs arrived at Perry Point, we'd pack them up and send them to the participating centers. In this instance, when the drugs came in, we noticed the labels from one company were an inch higher than the labels on the canisters from the other. If you had these on the shelf, you could immediately see there were two different kinds of drugs. In order for this to be a double blind study, we had to repackage all that stuff to make it uniform. Those were interesting days.

LH: A lot of chores besides grinding out numbers.

JK: Right.

LH: Sometimes I wonder if we did massive scientific overkill, because these drugs were so effective compared to what we had before and so altered

the natural history of the illness that it hardly seemed necessary to do such elegant trials.

JK: That's true in some respects, but not in others. Shortly after I arrived, I used the data from Project # 1 in a sequential analysis and, with eight patient pairs, reached a statistically valid decision on the relative efficacy of Thorazine (chlorpromazine) vs. Phenobarbital. That study went on for another year so we ended up with 600 patients, but for good reason, we needed to have data on side effects and other stuff, as well. But, in another case, our large sample sizes haven't helped us in the search for "the right drug for the right patient" which is a clinically important question. NIAAA just did a huge $27 million study called "Patient Match" directed at that.

LH: To find the right treatment for the right alcoholic?

JK: They didn't have much better success than we did. Even with these large samples, we could not detect differences easily between many of the new compounds.

LH: You were working on your side and John and I were working on ours, so I don't know who thought up the title of the paper, "The Right Drug for the Right Patient." It was an illusive search.

JK: That was my paper and I thought it was a catchy title.

LH: It expressed the whole search so well. That was the beginning of a growing echelon of people applying advanced statistical methods to psychiatric and psychological problems, which spread into other fields. I'm sure the large studies on anti-hypertensive drugs and coronary surgery used the same techniques.

JK: Probably about the time we got started, the first VA hypertension trials were on the drawing boards. Interestingly enough, while we were doing our thing in psychiatry, there was another group of people, in Baltimore, doing multi-center trials in diabetes.

LH: That was the University Diabetes Group. Boy, that was a controversial group.

JK: It sure was, but drawing from that nucleus of people, they founded the Society for Clinical Trials and the Journal of Clinical Trials, which is a first-class journal and organization that attracted a lot of the biostatistician types. Jerry Levine, Gerry Klerman and I participated in one of their annual meetings. Nobody in that organization ever got into the mental health area at that time, and I don't know they have since, because they had their own focus, diabetes and other disorders. But the statistical methodology papers were interesting and important.

LH: The laboratory at Perry Point dealt with all sorts of trials until they set up several other laboratories.

JK: For the first 15 or 20 years, we focused exclusively on neuropharmacology trials. But, the VACO Research Service was reorganized and we got pulled into a different orbit, and began to do trials in a lot of different areas. When Dr. Baker, Chief of Psychiatry died the commitment of Central Office Psychiatry diminished. There wasn't that kind of interest in the program. We missed some good opportunities then. The VA could have done good epidemiological work on tardive dyskinesia, issues like that, but they were left to others.

LH: But, it wasn't all drugs either. There was that study Margaret Lynn honchoed on sociological aspects.

JK: I expect that you'll be talking to Sam Kaim sometime soon, through Sam we got involved in research on substance abuse. Shortly after he joined us, we did a study of alcohol withdrawal and DT's. which was picked recently by NIAAA as one of the seminal articles on alcohol research in the last 25 years. It's a nice compliment to Sam. We were also ready to move into the area of drug abuse. Jerry Jaffe had been picked by President Nixon to head the Special Action Office for Drug Abuse Prevention. One of his jobs was to pull together all the research being done in various agencies, including the VA, and centralize it. His main interests were to develop a long acting maintenance medication for heroin addicts, a long acting methadone, and another one was naltrexone, a narcotic antagonist. These two pharmacological approaches were part of his goal. We did organize a trial of LAAM, but before it started, Sam Kaim retired from the VA and went to the National Research Council so we needed a Study Chairman to replace him. I had been working with Walter Ling, a person of great energy and I felt he was ideal for the job. That decision has paid off immensely since.

LH: That first study of LAAM was in the middle of the 1970's, wasn't it?

JK: Yes, and it eventually turned out to be the pivotal study for the approval of LAAM. It took years for the FDA and NIDA to get that done.

LH: About 18 years.

JK: That's another story, which we don't have time to talk about. But it is important the study provided data on which the FDA based their approval of LAAM, and it is now available as one of the treatment options. Walter and I have been working for some years on buprenorphine, another maintenance medication for heroin addicts, and the data we've generated is going to serve as pivotal in the approval of the new drug application for buprenorphine. That area of research has been very interesting and productive; it has always been a joy to work with Walter and I'm still working with him.

LH: I know.

JK: I have to close that loop. Sam Kaim went over to the National Research Council and headed up a committee on the development of the heroin antagonist, naltrexone, and chose you, me and Danny Freedman with others to serve on it. We managed to do our job and put naltrexone in the proper perspective so it was shortly approved by the FDA.

LH: I honchoed a committee to study that. We did the first controlled trial but had to sweat to show a difference.

JK: That study focused on street addicts already in methadone maintenance and people in work release programs. The problem we had was to get people clean before they could be switched to naltrexone, so we'd start off with hundreds of patients and end up with a very low yield. Then they'd get naltrexone and drop out within the first six weeks, so it was very discouraging.

LH: It was not like methadone, where you're hooked. However, naltrexone has resurfaced as a very effective treatment for alcoholism. It is being used more for alcoholism than for heroin addicts. Well, when did you retire?

JK: January 1988. So, I've been retired from the VA for almost 10 years.

LH: Did you still act as a consultant for a NIDA committee?

JK: Oh, yes. There were times when I wasn't sure if I worked for the VA or for the Institutes of Health. I was on one committee or another for 20 years. A lot of us made that kind of commitment. I was on the NIMH Clinical Research Centers Committee for 4 or 5 years after I retired, a very interesting assignment. And I had other commitments. I was on some data monitoring boards, such as the VA clozapine study and on the NIAAA Patient Match Study. Shortly after I retired, Walter Ling said, "Let's put in a grant to NIDA for one of these Clinical Centers in Drug Abuse." By then, Walter was in private practice and I was retired.

LH: What a way to start a grant!

JK: Initially we got a large 5-year grant. I don't think NIDA has ever given a grant to two people whose credentials were so thin. But Walter is now a full professor at UCLA and he's certainly done very well.

LH: Ever since you began, and even earlier, the randomized parallel group double blind design has been the gold standard for assessing drugs and these studies can be expensive and laborious. Do you foresee the development of techniques that might be less laborious, less expensive?

JK: I've read some things Don Klein has written about doing clinical trials, and although I can't repeat all the lessons he pointed out, I agree it would help strengthen Phase 1 and Phase 2 trials. But eventually there is need to do large Phase 3 definitive studies. Those will remain the

same, with some statistical and methodological improvements. I also think we need to go back to the time in which the people who designed trials spent a lot of time with patients instead of being on committees and flying around the country or to Nepal or someplace. For instance, NIDA has been screening all kinds of drugs, trying to find something for cocaine. Good clinicians have to talk to patients, ask them, "How does it make you feel?" Sometimes clinical trials have become kind of impersonal. A research assistant recruits the patients and they fill out some forms but you don't have a wise sensitive clinician who talks to the patients. That is one lesson more attention could be paid to. .

LH: They were victims of their own success; they have been very effective in sorting drugs out, but nobody wants to risk trying anything new, so you get locked into a system.

JK: Yes, there is that. I was reminded that you and John Overall did relatively small but quick studies, drug screening, to find rewarding compounds. I've been reminded of that many times since when people ask, "Is there some way we can do this quicker, easier? How about doing sequential analysis?" You might think that's a very appealing technique, but there are drawbacks applying it to studies in which the duration of treatment has to be extended before you know if you've got a winner. It hasn't really worked out very well in clinical practice, for that reason and because many Phase 3 trials have more than one objective because they need to generate a database for adverse reactions and so on for the FDA. Anyway, in response to questions about more efficient designs, I refer to your approach. If you want to screen a lot of compounds and be as efficient as you can, where you lose time is getting geared up, getting drug supplies and all you have to do for a six or eight week trial. You may spend a year getting organized, but you, John and your group did these small studies very efficiently. You were able to get one study started, and while that was being completed, you got another one organized. So you did a lot of work in a relatively brief period of time. That kind of efficiency, if you're in the business of screening compounds for activity, is the way to go.

LH: Right now there's a huge controversy about the medical uses of smoked marijuana and oddly enough there are no controlled trials. But it's simple to devise a new kind of approach; you could have a placebo for the cigarette and for the oral capsule, both of which have been available for years, set them up in groups of four, randomize within the groups and do a retrial of chemotherapy. Of course, you have a very effective antiemetic in case it fails so it wouldn't cause the patient too much trouble. You could settle that issue quickly and clearly.

JK: That's true but who would fund it? I'm not sure the authorities are anxious to approve marijuana for medical use.

LH: No, but I think the political pressure is going to get so great they will have to fund it. With States taking action into their own hands they are making decisions about approving drugs as therapeutic agents based on insight, rather than science. What doesn't make sense is when voters say, "It's O.K."

JK: What's the active ingredient of marijuana?

LH: THC

JK: That's available in a pill, isn't it?

LH: It's already approved.

JK: Sure, but the consumer isn't interested in taking a pill. Don't they want to smoke?

LH: There are some disadvantages to the pill, even if you're going through chemotherapy. First of all, the capsule may dissolve at different rates and you have to time it to get the effect when you take the chemotherapy. The second thing is, you may need more than one, so when do you take the second one? The pharmacokinetics when you smoke marijuana is like an IV injection, you got the effect immediately, so that makes it different. But, people are not going to rest on the availability of the oral drug; a lot of people want to smoke the drug. And, I think there are ways to test it without using a conventional design.

JK: You would want it blind, wouldn't you?

LH: You could make a blind trial, but it wouldn't be a parallel group design within patient, that's because you have to assume that every dose of Cisplatin is going to cause the same amount of trouble for the patient. You get into the problem of conditioned nausea and vomiting, but if you started off before they ever got conditioned, you could avoid that.

JK: That design might work for that application or in the case of analgesics and pain tolerance, where you get a quick answer. There you might use Latin square or repeated measures for crossover trials efficiently, but not in the usual application with depressed patients or schizophrenics where the response time is much longer. There we're stuck with the parallel groups design.

LH: Would you have chosen the same career all over again?

JK: Absolutely! I've really enjoyed the intellectual challenges and the people I have worked with. There are a lot of people I haven't mentioned who have been important in my career. You didn't ask me how I got into ACNP. Jon Cole told me I ought to be a member so that's how I came to join. Also, Jon was at the Psychopharmacology Service Center and

asked me to be a member of his committee for grant reviews. So he gave me a first step up in several ways, and there were others like that.

LH: What do you see the chances of replacing people like you and John Overall, the pivotal pioneers in the field of statistics applied to psychopharmacology? Are we getting enough new people to keep the field alive and flourishing, or should the ACNP take a more liberal policy toward admitting people in this discipline?

JK: It is important to have people represented in the membership but it doesn't always work out that way. I sponsored Phil Lavori on two occasions.

LH: He's good.

JK: He's outstanding. There ought to be an attempt to recruit people like Phil and some others because the organization needs it. Remember, the teams we used to have, with you and John and Gene Caffey and myself. Phil is working with Klerman and others on the depression studies. ACNP needs people who can work together with clinicians and bring a lot of expertise in quantitative work, so there should be some outreach to get them in. Now, they're not replacing people like John Overall. These positions are being filled by bio-statisticians, PhDs in statistics, and that's alright but they don't come with a background in psychopathology the psychologists tended to have, or as much interest in the subject matter.

LH: People cross disciplines all the time, as you did, so even if they came from a purely statistical background you could give them know how in time.

JK: Sure, in time, especially if they make a commitment to working on psychopharmacology problems. There's a woman statistician at Palo Alto, Helena Kramer. She's now a member of ACNP, I believe.

LH: Some of us feel, in that field, there is a gap in the membership developing where it's not representative enough. These guys doing basic work grind out references by the dozens. They'll come in with 36 published papers. That drives all the rest of the people for cover, because you can't do that as a statistician. You can't do that as a clinician.

JK: But, Leo, another thing has happened in the past 30 years or so. When I first arrived on the scene, wet behind the ears, if I described how you could do a chi-square test, people would oooh and aaah. The clinicians really needed help in those days. But the clinicians of today are a lot more sophisticated so they don't have the same needs for quantitative back up. Look what's happened to the computer field. All of this statistical stuff is in packages.

LH: Programs in a package!

JK: If you know how to punch a couple of buttons, you can get your statistics done.

LH: You may not know what to put in, though.

JK: You certainly need to have a statistician involved in the planning and conduct of the trial. But, there have been some important changes of the kind I just mentioned.

LH: Even so you can always get these program statistics, there are underlying assumptions on each one that are very often neglected, so people use the statistics without meeting the underlying assumptions. You still need somebody who knows more than how to push buttons.

JK: John Overall is a good example of a person who knows how to use statistics creatively. John would always come up with interesting twists on looking at numbers. That's one of his strong points.

LH: I've called John a national treasure, in the same way they have national treasures in Japan. One of the things I can say is, I've had sense enough to know when I needed help, and John's been an enormous help. Nice going over all the trials with you Jim. What's the old Pennsylvania Dutch saying, "We go all too soon and smart too late".

JK: Something like that.

LH: I felt stupid throughout most of my life. Now that it's beginning to get to the end, I feel a little better about it.

JK: You and I share a lot of memories, but one thing we share is that we were part of the VA in the early days. That era has passed and people who are newer to the field may not recognize the important role the VA played in those years. So it's good to get that on the record.

LH: That's why I wanted to have you, Clyde, Sam and some of the other people go on record, because in terms of the pioneering effort the VA made, it never got as much credit as it should have, and that's a pity. Well, happy retirement! I'm going to join you soon.

JAMES H. KOCSIS

Interviewed by Joel Braslow
Waikoloa, Hawaii, December 2005

JB: This will be an interview with Dr. James Kocsis* for the archives of the American College of Neuropsychopharmacology. We are at the annual meeting of the College in 2005. I'm Joe Braslow. Please tell us something about yourself.

JK: I am Professor of Psychiatry at the Weill Cornell Medical School in New York City and I've been a member of the ACNP since 1986, for nearly twenty years. The work that I'm going to focus on is in the area of dysthmia and chronic forms of depression, what has been the major theme of my own work over the past twenty-five years. To put this into a larger context, between 1960 and 1980, the year DSM-III was published, there was a movement in to redefine psychiatric disorders and a shift in the understanding of them as biologically and genetically based, as opposed to being psychological and based on early life experience. There were older diagnoses known as depressive neurosis and depressive personality disorder that today we would think of as having dysthymia. These are people who begin to be depressed in childhood or adolescence and remain chronically depressed. They may also develop periods of major depression during their lifetime.

JB: So, they've been that way all their life?

JK: I've been that way all my life. I'm a melancholic person. That's the way I am. That's my nature.

JB: You have been at Cornell since 1986. Was that your first faculty position?

JK: I've been at Cornell since 1964. I graduated from Amherst College and entered Cornell Medical School in the fall of 1964. I graduated in 1968, and did my residency at the Payne Whitney Clinic from 1969 to 1975.

JB: Why did it take so long?

JK: It was the Vietnam War era and I was drafted into the military for two years in the middle of my Psychiatric residency. I completed my residency after I came back.

JB: Were you in Vietnam?

JK: No. I fought the Vietnam War in Virginia Beach for two years, tending to the wives and children of sailors. I was functioning as a general medical officer, not as a psychiatrist, because I had not completed my residency. I never set foot on a ship and did not go to Vietnam during my two years

* James H. Kocsis was born in Torrington, Connecticut in 1942.

in the Navy. But I learned a lot about general medicine and a lot about depression. There were many Navy wives who were depressed when their husbands were deployed overseas in the Mediterranean or Pacific and they got more depressed when their husbands came home. They were not used to having them around, demanding and wanting to be waited on.

JB: Is that what sparked your interest in depression?

JK: That was one of the things, particularly in antidepressant medications. These women didn't come into the clinic and say, "I'm depressed", but instead, "I have headaches, backaches, stomach aches, I'm crying all the time and I feel like killing myself". When you talked to them they met the criteria for major depression, as we understand it today. I was assigned to see a patient every fifteen minutes from 7:30 in the morning until 4:00 in the afternoon. So, I didn't have time to psychoanalyze them. Instead I put them on a tricyclic antidepressant like Elavil (amitriptyline) or Tofranil (imipramine) and the next time I would see them might be three weeks later, for another fifteen minutes. And, lo and behold, a lot of them got a lot better.

JB: Did that surprise you?

JK: It did.

JB: Tell us why.

JK: Because I was not a believer in any particular ideology about depression. I understood it could be based on life events, personality characteristics, psychodynamic issues and so forth. But I was very surprised to see how dramatically beneficial antidepressant medications were for these women dealing with very complex issues. I became known as "Dr. Elavil" at Oceana Naval Airbase Dependant's Clinic between 1970 and 1972. A similar experience I had was as a medical intern at the James Ewing Hospital in New York, the city's cancer hospital for indigent patients, part of the Memorial Sloan Kettering Cancer Center. It was like the old Bellevue Hospital in New York with overcrowded big wards. As an intern or resident you had to wheel your own patients around on their cots to go to X-ray or for tests. Additionally, we did all our own blood drawing and so forth. These patients were very ill with severe forms of cancer so, again, I began to administer antidepressant medications without a great deal of optimism or enthusiasm.

JB: Why was that?

JK: Because they were so ill and had such a real problem; many of them knew they were going to die.

JB: What are the prevailing ideas about depression and chronic medical illness?

JK: There's some truth that if you have a severe stressor, medical illness or so on, you may be less likely to respond well to treatment with anything. But what amazed me was that many of these patients did respond favorably to tricyclic antidepressants. These two experiences were the background to a lot of my research concerned with redefining the conceptualization of different types of depression and testing whether they would respond to pharmacotherapy. So my first grant from the NIMH in the early to mid 1980's was for the first prospectively designed randomized clinical trials of antidepressant medications in dysthymia.

JB: What did you do after your residency?

JK: I went to work for one my mentors, Dr. Peter Stokes, whom I eulogized in the Memorial Symposium here today. He's one of six or eight ACNP members who've passed away within the last year. He was a leading early researcher on the biological aspects and pharmacologic therapy of depression and bipolar disorder. I did research with Peter when I was a resident and went to work for him as a junior investigator and assistant professor at Cornell when I finished residency in 1975.

JB: So you planned to have a research career all along?

JK: That's an interesting question and the answer is yes, because I went to medical school with the intention of doing psychiatric research.

JB: Why did you choose that path?

JK: Personal history, perhaps. A grandfather, my mother's father, who had recurrent major depression, was treated at the Institute of Living in Hartford with ECT in the 1940's and 1950's. Then, as an undergraduate at Amherst College, I volunteered at the Northampton State Mental Hospital in Massachusetts. As a historian you might want to see a movie, called *Titicut Follies*. Have you seen it?

JB: Yes.

JK: Titicut Follies was filmed at Bridgewater State Hospital, which was another hospital in the Massachusetts state system and it shows what I saw at Northampton when I volunteered as an undergraduate. It became obvious to me that the most interesting and important thing you can do in psychiatry is research, because, even if our knowledge of these disorders is primitive, there are many things we can do to help patients. So I've maintained a lot of excitement and interest in doing psychiatric research.

JB: When you entered psychiatry psychoanalytic influence was about to wane with the rise of a biological viewpoint. How did that shape your desire to do research?

JK: Although I was at Cornell, the two important influential people on my early thinking were not. One of them is at this meeting and also spoke at

the Memorial Symposium. He is Donald Klein from Columbia. The other one was Hagop Akiskal, who used to work at Memphis. Now he's at San Diego.

JB: How did Don Klein and Akiskal shape your thinking?

JK: Both defined what I was interested in. Don used the term, chronic characterologic depression, to describe the people I'm talking about who have early onset, chronic lifelong depression, and made the observation that many responded very well to MAO inhibitors. But this was a clinical observation, not based on research. Similarly, Hagop defined these people and rediscovered the word dysthymia in the late 1970s when he described a group of patients with chronic, mild, lifelong depression. So, those ideas had a lot of influence on my thinking and research. Also, an important influence was the debate in the late 1970s about whether chronic depression should be a personality disorder (Axis II) or a mood disorder (Axis I) in DSM-III. This was a big difference in terms of how to treat it and what kinds of research needed to be done.

JB: And the differences in research are?

JK: If it's a personality disorder, the main approach is going to be psychotherapy and looking at early life history and experiences and not so much at biological issues and pharmacologic treatments.

JK: Were you personally involved in that debate?

JK: I was too young at the time to be a figure in that but I got onto the mood disorders committee for DSM-IV. I was old enough and influential enough by that time, but not when DSM-III was prepared. What happened was that the affective disorder guys won; chronic depression was named dysthymia and put on Axis I in the mood disorder section.

JB: How was that decided? Was it science, politics? How did you see at the time and how do you see it now?

JK: It was largely a political decision. It was a committee decision and there were influential people on the committee like Akiskal and Klein who carried the debate, and probably Gerald Klerman was also influential. The consequences lasted for the next twenty-five years, because there's still no depressive personality disorder in the DSM. So, anyway, I did the first placebo controlled trials of antidepressant medications in dysthymia and chronic depression.

JB: And, that had a fairly big impact?

JK: That's probably the work that got me into the ACNP in 1986. I had my own independent grants and line of research and began to make a name in the area. I have been working on offshoots and ideas from that work ever since.

JB: Despite some more selective drugs introduced you stayed with imipramine in your research?

JK: Right.

JB: Why didn't you use some of the newer drugs?

JK: I had in these studies important collaborators like Alan Francis, Gerald Klerman, John Mann, and, in the early 1980's, our interest was not to discover a new drug, but to show that antidepressant medications worked for these people. A lot of clinicians didn't believe they did. They didn't even believe these people had affective illnesses. They thought they had something else and the patients also believed that. They thought they were misdiagnosed and went to medical clinics and internists who ordered all kinds of X-rays and tests. After getting the results they'd say, "I'm sorry there's nothing wrong with you, it must be in your head". But they didn't diagnose them as depressed and they didn't put them on antidepressant medication.

JB: Would it be fair to say your findings increased the use of antidepressants in general medical practice and was critical in shifting treatment priorities in dysthymia?

JK: That's a fair statement and over the last twenty-five years I've done a lot of lecturing and teaching internists and primary care physicians who are not psychiatrists. I have been educating them that they have a lot of depressed patients and chronic low grade depression is easy to miss because you only pick up the somatic symptoms they complain about. You work them up and the work-ups are negative; they're frustrating patients because they don't go away, but if you diagnose them as depressed and put them on antidepressant medications, lo and behold, miracles happen and they get better. They're happy and you're happy. That has been an important evolution from work.

JB: After you published the findings what happened next?

JK: There is a chronological sequence to research. The first thing you need to do is a short term placebo controlled trial to show that something works in the short term. The next study, which takes five years to do, is on long term maintenance to answer the question, "Now doctor, if this antidepressant medication helps, do I need to stay on for the rest of my life?" These are chronically depressed people, so we need long term studies. That was the next phase, to do maintenance studies and discontinue medication at various points to see whether all the patients would relapse or you could cure dysthymia by treating it for three months or six months? In recent years we've been getting into studies with treatment refractory patients. But before I get into that, I should mention Peter Kramer who, in the early 1990s, wrote a book

called *Listening to Prozac.* It was on the New York Times Best Seller list.

JB: How did you feel about that book?

JK: It's a very good book.

JB: Have you read his most recent book?

JK: I have not.

JB: I think the title is *Talking Back to Depression*.

JK: I've not read that. *Listening to Prozac* is a series of case vignettes, clinical anecdotes about chronically depressed dysthymic people. He put them on Prozac and for the first time in their life, they brightened up. They functioned better. It was like a personality makeover. So, there are a couple of issues. One is, what do you do in the long run? Do you keep them on Prozac forever? The other issue is the *Listening to Prozac* effect only occurs in about one-third of the patients. Another third don't respond and the final third get a partial response.

JB: The placebo response was usually what?

JK: The placebo response is low and that's true for anything that's chronic. Chronic illnesses have low placebo response rates which are good in a way, because you can be assured that if they get better, it's probably what you did that made the difference, whether it's psychotherapy or medication. In recent years we've become involved in developing sequences or algorithms of treatment to determine what to do if the first medication doesn't work. Interestingly, one of the "then do what" treatments in my current NIMH grant is a form of psychotherapy. It is an eight site study of psychotherapy augmentation for treatment of chronically depressed patients who do not respond to an initial trial of medication.

JB: What kind of psychotherapy?

JK: You probably are familiar with cognitive behavioral therapy, CBT. It's fairly popular and widely practiced, particularly among psychologists for treating depression and anxiety disorders. Some cognitive behavioral therapists attempted to do CBT with people who are chronically depressed and found it didn't work very well. It worked better in acute or recurrent depression, but not for the always glum, depressed individuals. A psychologist, James McCullough, out of Virginia Commonwealth University in Richmond, modified CBT for patients who are chronically depressed. It's called Cognitive Behavioral Analysis System of Psychotherapy or CBASP. It is behavioral therapy with psychodynamic elements. They got rid of the cognitive parts of CBT that focus on helplessness, hopelessness and worthlessness issues. We tested CBASP in a very large study of chronic depression and our findings were published in the New

England Journal of Medicine, which is unusual for a psychiatric study in 2000. Martin Keller, who was Chairman of Psychiatry at Brown, was the first author. Subsequently we submitted this protocol for an NIMH grant, which was funded three years ago. I presented the preliminary results at this meeting yesterday. We're treating about a thousand chronically depressed patients with antidepressant medication and then randomizing the non-responders and the partial responders into augmentation with CBASP vs. augmentation with standard supportive psychotherapy vs. continuing medication only. This is the first study that has looked at attempting to augment antidepressant medication non-responders with psychotherapy. And we all agree that it works. For chronically depressed patients, standard forms of psychotherapy, like CBT, supportive therapy or psychodynamic psychotherapy tend not to work very well. So we think CBASP offers something unique and specific. It's more potent as a psychotherapeutic approach for patients who don't get completely better with an antidepressant alone. One of the other issues that came out of the CBASP study has to do with a history of early life trauma and abuse. Many chronically depressed people have early life adversity, trauma and abuse that have some interesting biological consequences. One of them, over activation of the pituitary-adrenocortical system, has been presented at this meeting. So we're interested in sub-grouping chronically depressed people according to whether or not they have a history of life trauma or abuse and studying which treatment they respond to best. That gives you an overview of where we've been, what we're doing and where we're going.

JB: How about for you personally? Have your views changed about the nature of depression over the years? You started off trying to parse dysthymia as a medication responsive entity, and in some sense you are going back on that.

JK: Come full circle?

JB: Yes. I'd like you to reflect on the trajectory you have taken and whether you think the field has taken a similar trajectory?

JK: Another way of looking at what you've said is that as we get older and more sophisticated we realized things are more complicated than we thought. In the 1970s, at the beginning of the biological psychiatry era, we felt the answers were right around the corner. That we were going to do spinal taps, to look at certain chemicals in the cerebrospinal fluid and tell which patient would respond to which medication. That didn't work out, things are more complicated. There are complex interrelationships between life experiences and biology. Early life experience may be relevant not only for psychotherapy but also for which medication

you need. So, instead of being in a battle, the disciplines of psychology and behavior are working in concert with biologists and geneticists to understand what's going on.

JB: How about you, personally? You talked about your earlier experiences that motivated you to go into psychiatry. In the course of your research career what excited and propelled you along?

JK: Research always excited me, whether it's my research, sitting around brainstorming with colleagues and collaborators, coming to meetings like this and hearing what other people are doing, thinking or discovering. In many ways, progress has been slow and there remains a lot to be done, but there's been a complete change in the landscape of clinical psychopharmacology during my career over the last twenty-five years.

JB: There has been a change, can you describe it?

JK: The drugs we were using in the 1960s have gone away. The MAO inhibitors, tricyclic antidepressants, barbiturates, you name it. There have been great advances in all areas of psychopharmacology.

JB: So, you feel what we see are advances? In concrete terms, do you find that the newer antidepressants are more efficacious than the old ones? What has been your experience?

JK: A lot of advances have been made in terms of safety, toxicity and lack of addictiveness. If you take a look, as an example, at the newer sleep medicines, I believe they're much safer and less addictive. Barbiturates and Miltown, (meprobamate) had efficacy but both were very addictive. If you look at antipsychotic medications, the advantage of the newer drugs is mainly in safety, for example, lack of tardive dyskinesia.

JB: What do you make of the more recent medications?

JK: There's a lot of controversy because some have different toxicities from the old ones, for example the metabolic syndrome, but not all of them, so they definitely represent an advance.

JB: Have you thought about the fact antidepressants are also a huge market? What has been your relationship with industry? How have you felt about issues that have been in the press, for example suicide with SSRIs?

JK: In spite of controversies and difficulties the pharmaceutical industry has presented, they have, in many ways, done the best research and maybe led to most advances in the field of psychopharmacology over the last twenty-five years.

JB: Could you specify those advances?

JK: Just developing the newer generation of drugs we're talking about, they all came out of the pharmaceutical industry. They haven't come from

academic medicine or federal grants, for the most part although there may be some exceptions. A lot of people in academia and government have been involved as advisors, collaborators or even moved to work in the pharmaceutical industry.

JB: How about you, personally, what has your relationship been?

JK: I've been collaborating with and advising pharmaceutical companies on development of new antidepressants and mood stabilizers for bipolar disorder.

JB: When did you start?

JK: Do you remember Asendin (amoxapine)? That was the first norepinephrine reuptake inhibitor.

JB: And who made Asendin?

JK: It was made by Lederle.

JB: Did you do some work with them?

JK: I put in an investigator initiated proposal to do a study of Asendin vs. Elavil.

JB: This was when?

JK: In the early 1980's. It was supposed to have an acute and a continuation phase and we had about eight different outcome measures, maybe four in the acute phase and four in the continuation phase. And we found Elavil beat Asendin on six out of eight outcome measures. This study was funded by the company that manufactured Asendin. I was a little worried, number one, that they wouldn't let me publish it and two, if I did publish it I'd never be welcomed or have another collaboration with any pharmaceutical company for the rest of my life. I was worried I'd be blackballed. And guess what; neither happened. They did allow me to publish it. It was published in the Journal of Clinical Psychopharmacology in the late 1980s.

JB: I see.

JK: They had some internal problems over the fact they funded a study that ended up making their drug look bad. But they never gave me any trouble over it. I've done many subsequent studies with other pharmaceutical companies and it never caused a problem.

JB: There's been a lot of press about publication of negative trial results and also of not allowing investigators access to data.

JK: I have experienced that once or twice. I've been frustrated by not being able to get negative studies published.

JB: Can you talk about that?

JK: I'm not going to mention any specifically.

JB: Can you talk about it, generally?

JK: Investigators lose interest and excitement when that happens. There should be a journal for negative results. Many people have said that to document negative results should be a requirement.

JB: You may or may not know there is, before both the Senate and the Congress, a bill called the Fair Act bill, meant to make all clinical trials public.

JK: I think all clinical trials now have to be registered and I don't know whether it's already a law or not, but they will be archived and documented. Maybe that's the law you're referring to.

JB: This law hasn't been passed yet but it will be much more stringent. You will have to record hypotheses and have to present the raw data afterward.

JK: I'm absolutely in favor of that, because it gives a much more accurate perspective on exactly what the efficacy is for the various drugs.

JB: You mentioned a couple of studies in which you were unable to publish your findings. Tell me more about that.

JK: I can't tell you too much more about it. They were dead in the water. People lost interest in them. Often times the people responsible for them at the company were either fired or left, and since they were gone, there was nobody to contact or talk to. There probably was quite a lot of that kind of thing and I'm sure that's what motivates the legislation you're talking about.

JB: So, during your career you had positive and negative interactions with industry. Could you tell me about the positive aspects?

JK: The positive aspects are that they've done a lot of interesting and important research with their drugs.

JB: And, for your career, specifically?

JK: A lot of my career has been spent doing Phase IV clinical trials, looking at applications of already approved antidepressant medications to populations like dysthymia and chronic depression. The CBASP study that was published in the New England Journal of Medicine was a study that had more than six hundred patients and it was funded, believe it or not, by a drug company. So that was very beneficial. I also had, in the early days of sertraline, a positive experience with the company that developed it. Pfizer had a very wonderful Phase IV clinical research program and they did a lot of great studies with diseases like PMS, PMDD, chronic depression and various anxiety disorders. Another positive thing is that research dollars available through the pharmaceutical industry dwarf the amount available anywhere else. So, if they ethically collaborate with good investigators from the academic community good stuff can and has come out of that. The bad side is that sometimes you

feel you're being pushed around by people from marketing or there are internal politics that end up destroying a study. Like anything in life there are pros and cons to.

JB: You have a lot more of your career left.

JK: I'm age sixty-three, so that's an interesting question for me.

JB: How much do you want to accomplish in the remainder of your career?

JK: I have no plans to retire. I am writing grants and formulating new projects at the present and I have it in mind that I would like to keep doing this until I'm about eighty, so that gives me quite a few more years. There are people who do that. The answer is to discover things sequentially little by little, to make small steps to advance our field and, in the area I'm interested in, do research with antidepressants that work through some novel mechanism. There are a lot of candidate drugs for such research. Many of them are being talked about at this meeting. Many of them are now at the level of mice and rats and not yet ready for human testing.

JB: Well, we covered a lot of territory.

JK: We have and we've spent an hour.

JB Anything you want to add?

JK: No, I think that's good.

JB: So, maybe in fifteen years, we'll do this again.

JK: Thank you.

JB: I enjoyed it very much.

YVES LECRUBIER

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 10, 2003

AT: I am Andrea Tone. It is December 13, 2003 and we are at the annual meeting of the ACNP in San Juan, and I am interviewing Yves Lecrubier.* Why don't we start, at the beginning and have you tell me something about your upbringing, childhood, early education?

YL: Well, my early education was in Spain when I was 8 - 12. So I learned another language early in life. And then in France we have a very classical education, oriented more towards literature than science. By going into medicine and understanding how our brain functions, I moved towards an interest to psychiatry.

AT: So when you began medical training did you see yourself becoming a psychiatrist?

YL: I didn't know at that point. But brain oriented certainly.

AT: What time period did you begin medical training?

YL: The year I started was 1964. This was just after the discovery of the new drugs, although I'm not sure that had a major influence. But, the fact there was a physiology of the brain that could be affected in a manner that benefited patients might have had an impact.

AT: So what did the medical curriculum in France offer students? We know that in the United States there were a lot of schools still wedded to the psychoanalytic model at this time; that a lot of people who became prominent in neuroscience were really turned off by the idea of spending the rest of their lives on the couch talking Freud.

YL: Education in France is always handled by the state. Medical school is a seven year course and at the end you have an internship. Then you choose a specific specialty. A psychoanalytic career is totally independent from the university; there is no real control or formal curriculum although psychoanalysts have a strong influence in France. There is a curriculum for becoming a psychiatrist and I'm interested in psychology, as all psychiatrists should be.

AT: So when you were in medical training in the early 1960s, they were already emphasizing the importance of drug treatment and biological psychiatry?

YL: Drugs were already available and we were looking for their mechanisms of action. So that was a rather interesting period, trying to understand why some drugs could improve specific disorders. That was a

* Yves Lecrubier was born in Algiers, Algeria in 1944. Lecrubier died in 2010.

challenge, so everybody thought that by understanding the physiology of the brain, one might learn how these new drugs had their unexpected therapeutic effects.

AT: Were there specific fields or challenges that interested you when you gravitated toward psychiatry?

YL: When I started a major surprise was the possibility that some schizophrenic patients could be substantially improved and have a life outside hospital. So that was of a great interest. From the start I had two areas of expertise, one in psychopharmacology and the other in psychiatry.

AT: Were you seeing patients?

YL: I was seeing patients but in parallel I did research with the pharmacologists and teaching in psychopharmacology.

AT: What were some of the first clinical trials you did and what do you consider some your most important early research?

YL: My early research was in depression. Patients have a problem with mood, but also what we call retardation. There is loss of energy, the patient moves slowly and if one speaks very quickly the depressed person has difficulty understanding and problems concentrating. We felt that independent from the difficulty created by their mood, it was retardation that made them ineffective. We also felt that retardation was their most biologically related symptom. We could also show that retardation disappeared when a person was successfully treated with an antidepressant. When you were treating them with a benzodiazepine, an anxiolytic, some of the patients felt much better, but their retardation didn't disappear. So we could separate the mood dimension from the physical and probably biological dimension. Of course we had to produce a scale to measure this change that we called the depression retardation scale.

AT: When you said that there was a difference in efficacy between antidepressants and benzodiazepines in depressed patients were you talking about tricyclic antidepressants?

YL: Yes. Truly depressed patients need to be treated with antidepressants. But in those times there were lots of patients called anxious depressed, and it was not known where to set the border between anxiety with depression, or depression with anxiety. But we felt retardation was a good predictor for responsiveness to treatment. If you had some retardation, such as difficulty reading a newspaper or book, if you had to reread the same page two or three times because of poor concentration, if you were moving slowly, and if you were unable to cope with your usual activities, then we thought you were depressed and needed

treatment with antidepressants. If you didn't have these symptoms, benzodiazepines would work as well as an antidepressant.

AT: In your current work you are writing about co-morbidity. Today, people in general talk about comorbidity and we have a lot of drugs, like Effexor (venlafaxine) which are advertised to convince doctors that in depression, anxiety is working behind the scenes, and if you see anxiety it's probably depression. In your early work you emphasized the importance of distinguishing between the two. So it seems you moved in a different direction?

YL: Absolutely. In my early research I focused on depression rather than on anxiety disorder, and the challenge was to see what the targets for antidepressants were. I didn't think it was mood, it was retardation, comprised of concentration problems or what people now call cognitive problems. Antidepressants also help patients to cope with problems in daily life and strongly impact mood. Then, studies in epidemiology showed that the diagnosis of depression was not constant. You may have an anxiety disorder first when you are 16, 18 or 20, and then develop depression at 25. There is no contradiction in saying there is some specificity for antidepressants in depression and there is also usefulness in anxiety disorders because, as defined now, they also involve cognitive mechanisms. Anxiety disorder also includes patients with social phobia. That term doesn't imply you are continuously anxious but that there are circumstances when you become anxious. Anxiety is a consequence of not being able to cope with the environment. If you think about generalized anxiety disorder (GAD,) its new DSM-IV definition refers to chronic worriers, to patients who worry about things they shouldn't. In the new definition there are specific triggers that induce anxiety. You qualify for GAD because you over worry, and not because you are anxious. The same thing applies for PTSD, post-traumatic stress disorder. You have flashbacks. You have this difficulty confronting thoughts of the trauma, the stressful event. That again is a mechanism that induces anxiety. In all these cases, anxiety is the consequence of some mechanism that makes a particular individual fragile. So the reason I have written that co-morbidity is the rule and not the exception, is because the risk factors that make somebody fragile may be common to depression and other disorders. It would explain why the same individual doesn't always develop the same disorder, but can develop different disorders in their lifetime. The difficulty is to understand why the same mechanism is expressed differently at any given moment. This is probably related to very simple things, for example,

age. If you imagine you are, let's say, 16 years old and not feeling well, what do you think is the cause?

AT: You're going to make me answer this question?

YL: Yes.

AT: Oh, boy, not doing well enough in school.

YL: Exactly. And you would probably be very careful whether your hair was appropriately cut, because if not people would look at you and you would be ashamed. So, if you develop social phobia that would be appropriate because of the kind of preoccupation you have at that age. Now, let's imagine that, with the same factors, you are not feeling well but you are 30. Then it's much more likely the cause is you are not coping as well as you should, that you have lost the ability to make your life what it should be. So you more likely become depressed. My idea is simply that the preoccupation you have at a certain age is strongly impacting on a common mechanism. The expression of that mechanism, whether anxiety or depression, depends on your age and environment. So that's why diagnosis is not stabile and why it is very important to acknowledge that co-morbidity is the rule.

AT: It's an interesting model, because it suggests that in addition to brain chemistry, environment and social mores about what people should and shouldn't be doing at certain time periods, plays a role in how a common mechanism is expressed. But it also depends on the culture one lives as to what a 16-years old female is worried about. How do you disentangle that?

YL: If you look at what happens in some of the Middle East civilizations, for example, the normal social way is that as long as you are a child you can speak and chatter. Nobody cares what you are saying because you are not considered an adult. So you are not responsible for what you say. Then, there is a ceremony when you are acknowledged of being an adult. And after that if you say something that is not appropriate, people will respond to it very severely. So after you are installed as an adult in society, you must be extremely careful what you say, otherwise you will be criticized and may develop depression or anxiety. That shows that triggers exist in all civilizations.

AT: So there are universal truths about anxiety and depression that may take on specific forms or manifestations depending on culture and conduct.

YL: Sure. And we still don't understand exactly what depression is. You may have many reasons for it. You have patients with bipolar disorder who have a manic followed by depressive episode. Clearly the origin of that kind of depression is different from the depression we talked about.

When I was referring to depression co-morbid with anxiety disorders or anxiety disorders co-morbid with depression it applied only to unipolar patients. Bipolar patients are different. Maybe in the future we will find that some of the unipolar patients are different from others as well.

AT: How would you say your work and findings have advanced the field in ways that other researchers have not. What makes your contribution unique?

YL: Who is really making a unique contribution? I'm not sure about that.

AT: Everyone says that.

YL: I'm in a field where many small things add up and the work of one person contributes to that of others. The fact we showed that in depression there was a dimension involved other than just mood, a very physical dimension, was an important contribution. The notion that there were physical symptoms of depression that you could measure and depression is not just a subjective feeling was important. After research in depression I moved on to do research in the field of schizophrenia. Since the research we did was in the field of psychopharmacology, we were interested in antipsychotics. At that period we were convinced that in schizophrenia there is a dimension of so-called positive symptoms, like hallucinations and delusions, another dimension that manifests as strange behaviors others cannot accept, and a third dimension of negative, deficit symptoms. All these deficits pre-exist, present before the first episode which is defined by the onset of positive symptoms. So the deficit symptoms are there before the first episode, and continue all through the patients' life, whereas the positive symptoms like hallucinations come and go. We emphasized that deficit symptoms are the most important component of schizophrenia, and that some drugs are better for deficit symptoms than others.

AT: Such as?

YL: Drugs that stimulate dopamine. Earlier on people believed that all antipsychotics needed to block dopamine. Since drugs which block dopamine can induce deficit symptoms while improving positive symptoms, we were the first to hypothesize that possibly in schizophrenia in some structures there was high dopaminergic activity whereas in other structures, and especially in the frontal cortex, there was low dopaminergic activity. Then, recognizing that neuroleptics, given in very low dose act as stimulating drugs, whereas, given at higher dose they act as blockers, we advocated it was possible to play on one or the other dimension by using the same drugs. Slowly what became apparent is that the major burden was from negative symptoms that were constant, and not from hallucinations. We contributed to the idea there was a possibility

of improving negative symptoms. At that time others were thinking that negative symptoms are irreversible and not a target for therapeutics. Our idea had an impact on opening up the field for having negative symptoms as targets of treatment.

AT: What other research stands out in your career as changing psychopharmacology?

YL: I discovered that only about about half of the patients had proper treatment. I realized that to improve mental health care the major challenges is not in finding better drugs but in improving treatment. By increasing the number of properly treated depressed patients by GPs in primary care from 10% to 30% you would have a 300% improvement. I moved my research in that direction even if it was, initially, not my expertise, because I thought that was a challenge.

AT: A public health challenge.

YL: Yes. And we have been working on trying to better identify patients for treatment. For that we developed an interview called MINI. That structured diagnostic interview has been very successful. All the previous structured interviews were targeting research and were lengthy two hours long. Realizing that a depressed patient cannot stand two hours of answering questions we moved to have a MINI interview that still gets 90% or 95% of the information that one gets in the long interviews. We showed that the answers in our 15-minute interview compared to the answers in two hours interviews are more accurate, because patients are not tired .The aim of the MINI is to facilitate the identification of patients. It has been translated into 45 languages at this point. That shows there was a need.

AT: My students are struck by how much variation there is in the practice and diagnosis in psychiatry in different countries. They want to believe psychiatry is a universal science that transcends national boundaries. So could you map out some of the key differences between France and other countries and tell us how you would address this issue of national differences?

YL: There are two very different problems. One is the difference between health care systems in the different countries. That does have a strong impact on psychiatry as with other specialties. The health care system in France is handled by the state. Reimbursement, until recently is almost 100% for severe illnesses, but only 70% for illnesses which are not as severe. So, if you have a very severe illness and need long-term treatment, you would be reimbursed 100%. So you can go to any GP or clinic as many times as you want. It's up to you, not to the system. The state is very reluctant to implement anything new because

it increases the cost of health care. The public is never fully aware of the cost; it is not well understood. There are other countries, like the UK where there is much more awareness by the public on what the difficulties are. For example, of the cost of a drug treatment or reasons for the long waiting time for an appointment with a specialist. There are major differences in how people see psychiatry, but there is stigma in all countries at different levels. There has always been stigma toward conditions where you have no treatment. When tuberculosis had no treatment, it was shameful to have tuberculosis, and you wouldn't marry your daughter to the son of a person who had it. As soon as an effective treatment was available, the stigma disappeared. We see that today for depression; with rather good results for antidepressants, the stigma is decreasing. Many people will go to friends or employers and admit, "I'm depressed." That means depression is relatively accepted but to a degree that varies from country to country

AT: I was interviewing someone two days ago who is an expert on geriatric depression in the United States, and learned if you are depressed over the age of 65 Medicaid won't reimburse psychiatrists well enough for them to take on an elderly patient. Drug costs are spiraling out of control so a lot of elderly people who are not affluent cannot afford the best or the newer treatments. It made me wonder whether it might not be better to be a person with a mental illness in a country with universal health care. Having grown up in Canada, I'm a big proponent of universal health care, but in terms of the patient, how would treatment vary for someone living in the U.S. versus France?

YL: Strangely, the major difficulty is not that different. A patient, regardless of whether they live in France or in the US, has only a 50% chance to be properly treated with an antidepressant. And that's very optimistic because the 50% are treated after an unacceptable delay, which can be years and not just weeks. In addition not 100% of the patients are treated with an appropriate dosage, so the proportion of those with optimal treatment would only be between 20% and 30%. That is just as true in the United States, France, the UK, Italy or Germany. So, for the advanced countries where you live is not as important. But the kind of drugs you will take may be somewhat different in the US and France. The cost of drugs is probably cheaper in France because the government has more control over the cost.

AT: Thinking about the state of the field when you entered it in the early 1960s, what do you think the key changes have been?

YL: First, that mental disorders could be improved by specific drugs leading to understanding that our brain was the origin of thoughts but that

thinking was just one of its functions. Then, the discovery that 30% of patients consulting a doctor have a mental disorder leading to the integration of psychiatry with the health care system.

AT: What are the key challenges facing psychiatry and psychopharmacology and where will the field will be 20 years from now?

YL: All those who predict the future have made major mistakes. But I believe we have enormous developments in neurosciences currently and an enormous amount of data. We don't know what to do with it, because we don't have a very good model for psychiatric disorders and a major problem is the lack of clinical research. We have lots of data generated in neuroscience and molecular genetics but only old classifications of psychiatric disorders. So, if we select, for example, depressed patients for genetic research we identify patients with a certain number of symptoms or above a certain score on a depression scale. This is not an adequate criterion for genetic research. So there are lots of negative results, because of the inadequate instruments we use for measuring change. We have no investigators any longer. Computers are analyzing collected data automatically but nobody thinks the computer is doing research. My feeling is, in the next years, we should disentangle psychiatric patients into relevant targets for research. In depression, for example, we should find out what different factors cause it and if we do we will end up finding specific treatments for each subgroup. This is possibly the future.

AT: Thank you very much. I enjoyed that.

YL: Thank you.

JEROME LEVINE

Interviewed by Samuel Gershon
San Juan, Puerto Rico, December 10, 1995

SG: This interview is for the ACNP History Task Force. One of the negative features of this endeavor is that both of us have been selected to deal with the historical perspective which clearly indicates we're too old to do something else! I am Samuel Gershon of the University of Pittsburgh and my guest is Jerome Levine.* Jerry, please introduce yourself more formally or fully and then we'll have a chat.

JL: My name is Jerome Levine, but most people know me by Jerry, and that's the name I prefer to be called by. I'm now Deputy Director of the Nathan Kline Institute for Psychiatric Research at Orangeburg, New York and Research Professor of Psychiatry at New York University.

SG: As this is a historical perspective we would like to get some insights both into your entry into the field, your role when you were leader of one of the branches at NIMH and how that activity related to the ACNP and the field of psychopharmacology.

JL: That's a great lead in, and gives me lots of latitude. I'm a psychiatrist by training and did my three years of residency, the first two years in Buffalo, New York and the last year at St. Elizabeths Hospital in Washington. Then, I owed two years to the Public Health Service and was sent to the Narcotics Hospital in Lexington, Kentucky. While I was there I got involved in trying to use LSD to treat narcotics addicts. Jonathan Cole who was head of the Psychopharmacology Service Center at the National Institute of Mental Health knew about this work because I had approached him for help in getting the data analyzed at the Biometric Laboratory at George Washington University, which he ran. Jonathan asked if I might come to NIMH and set up controlled trials to test the utility of LSD in treating alcoholism and some other psychiatric disorders. He was under a fair amount of pressure at that time, because claims were being made that LSD was a cure for alcoholism, psychoneuroses and what ever else ailed mankind. So, when I finished my two-year stint at Lexington, Jonathan invited me to join the Psychopharmacology Service Center (PSC) at NIMH.

SG: Could you say a bit about the attitude that existed at the time on the use of the hallucinogens for any purpose because people have opinions now that are very different from those that existed then but we're still dealing with some of those concerns.

---

* Jerome Levine was born in Brooklyn, New York in 1934.

JL: LSD and the hallucinogens or psychedelics were, in the beginning, a laboratory curiosity. They were drugs, LSD in particular, which worked at microgram quantities, whereas most drugs work at milligram amounts. Everyone was interested in how a substance could be so potent in the brain. You could give 50 micrograms of the drug and know that in 20 to 30 minutes you were going to see a variety of profound responses in the subject. You could induce an altered state of consciousness regularly by using LSD; hence it's classification as a hallucinogen, a drug that would induce a hallucinations or a psychotic state. It was a great laboratory curiosity for both basic scientists, because it worked at such microgram amounts, and it was interesting to clinicians because of the altered states of consciousness it induced. Timothy Leary and some other people at Harvard became interested in the drug, not as a treatment or a laboratory curiosity, but as a substance that could induce profound psychological changes which they believed lead to enhanced performance and interesting spiritual and religious experiences. So, they felt LSD was a boon for mankind and if virtually everyone could take the drug they would become better people. Hence, there was almost a cult that began to advocate its use on a wide spread scale. Since society considered taking LSD as drug abuse, a conflict arose between those advocating and those opposing its use outside the laboratory.

SG: How did it come about in this climate that there was pressure exerted on an official arm of government, the NIMH, to examine the LSD issue from both sides?

JL: That's what made it really interesting at the NIMH in the 1960s. There was a group of people: Humphrey Osmond, Smythies, and a group from Canada, who were utterly convinced that LSD could cure alcoholism, and they were publishing reports and giving talks that stated this. So the question about the therapeutic use of LSD became a public health issue. If LSD, in fact, was a treatment, it should be used more widely, and, if it was not a treatment, then people should not be receiving it or might even be charged for its use. And that's how the NIMH was influenced to set up these trials. But, then, there was the problem that if LSD is a drug of abuse, would legitimate research being done with it, lend to its credibility and spread its use?

SG: So, the governmental agency was essentially requested to make this therapeutic inquiry, and that's what was carried out.

JL: That's correct, and let me tell you what happened with the drug and how the government has been in the forefront of continuing the study of LSD. Sandoz, the pharmaceutical company that manufactured LSD and was the sole source of supply in the early 1960's, made it available

to any investigator who wanted to use it. But, as they came under increasing criticism because LSD became a drug of abuse, Sandoz said, we will no longer supply the drug to any investigator. We can't take the risk because it's besmirching our name. One day I got a call from Craig Burrell at Sandoz, who said Sandoz was no longer going to distribute the drug. We understand the need for making the drug available for scientific investigations that are underway so we are willing to offer NIMH our entire Sandoz supply of LSD. I said we would very much like to have that in order to provide the drug to researchers. As a result, one bright day an armored truck pulled up to our North Bethesda Office Center in Bethesda with that entire supply of LSD and they asked where do you want it? Luckily, I had made arrangements for it to be kept at the NIMH pharmacy so it was taken there. Then a joint NIMH-FDA Advisory Committee was set up, which received requests for the drug and passed it on to investigators. In his way the use of LSD was controlled by FDA, and its availability was through the NIMH. That committee continued to function for many years; a pharmacist, John Scigliano, ran it. I'm not sure how the system works now, but I know that psychotomimetic drugs are still available through the government to carry out research.

SG: Maybe we should move on to the role you played as a Scientific Administrator when you moved to the NIMH.

JL: The part of the NIMH I went to, the PSC, had extramural functions, which means it dealt with grants and contracts to support research, rather than having our own laboratories and clinical facilities. I liked that way of working very much. I had met a colleague at Lexington, Dr. Arnold Ludwig; he and I had done some of the LSD studies. When I left Lexington to come to NIMH, Arnold went to Mendota State Hospital in Wisconsin where he had the opportunity to carry out clinical trials with LSD in alcoholism. Being at NIMH with responsibility for setting up controlled clinical trials with the substance, I set up one there. There were also several other trials set up around the country. I realized that by opening up requests by grant applications, we could get a lot more research accomplished in the field than if we at the NIMH carried out the work ourselves. This was the whole principle of the extramural function. In those days, there were a sufficient number of people on staff at NIMH that you not only had the administrative function, but you could participate in the science of what was going on. So, Arnold and I saw ourselves as collaborators. Jonathan Cole set this template by recruiting people to PSC who could serve as knowledgeable administrators and continue to participate in science. People like Gerry Klerman, Nina

Schooler, Sol Goldberg, Ron Lipman, and several others were at the NIMH carrying out these dual functions. I joined the NIMH in 1964 and when Jonathan Cole's Deputy left, he asked me to be take that position. To my shock and disappointment, in 1967, Milton Greenblatt recruited Jonathan to become Superintendent of Boston State Hospital. So, when Jonathan left the NIMH, I became the Acting Director of PSC, by virtue of being the Deputy. Then, in about 1969, we had been reorganized and when the PSC became the Psychopharmacology Research Branch (PRB,) I became the Chief of that branch, a position I kept until December 1994.

SG: It would be helpful if you could talk about the accomplishments of PSC and compare the situation then and now.

JL: Those were very different days than now. The PSC had adequate staffing and funding. In fact, there were times when we had more money than we had meritorious research. That's when Jonathan and the staff were at their best in finding and encouraging people who might not have applied for grants to do some work. It was also unique and worthwhile that our peer review committees were adequately funded so we could go to the sites of proposed research and meet the investigators. This was not only good for the investigators, because they might not have presented well on paper, but it was tremendously educational for the site visitors to see what was going on. You could have confidence in decisions that were made because you saw the site and didn't depend entirely on a paper submission. You could also interact with the investigators; there was a collegial relationship that could help the project. Very frequently people would visit the sites two or three years later and saw whether their initial decisions were correct or incorrect. Collegiality and a kind of continuity ensued in the field, which I think has been responsible for a lot of its growth. Now, in 1995 and 1996, there has been a major downsizing at NIMH. There has also been an increase in the number of investigators and research sites. But, unfortunately, there is a very great shortage of funding. So we have many more well trained people who are able to carry out studies but not enough money for the kind of quality review, based on site visits that we were able to do before. I fear the deterioration in quality of the review process, may bring about some weakening of the field.

SG: I think that's very true. As a consumer, I feel that's a very important change that's taken place.

JL: Which change are you referring to?

SG: That previously the staff in your branch could give feedback to investigators and act as scientific colleagues, not just accountants. That apparently has been changed by legal mandate.

JL: I wasn't aware that it was changed by legal mandate, so I can't comment, but the fact is that because of the smaller number of people there isn't time for them to keep up with the science, to do the kind of visits necessary to keep current. And, the field is moving much faster now because of the larger number of people and increased technology. So the role of the NIMH staff has changed. There was also another change in the 1960s and early 1970s; in the old days the review process was run by the programs that funded the research, so you had both review and program functions together. Now there has been a separation, so the program staff is no longer involved in the review.

SG: That's what I was getting at.

JL: This, unfortunately, has not worked out very well because, after the separation of review and program functions, there wasn't sufficient funding to staff review to a high level of competence. This has, in my opinion, deteriorated the review process, which in the long run, will diminish the quality of what's being supported.

SG: That's what I was getting at and you've explained it clearly. I agree that these changes have adversely affected the growth of the discipline. So, let's go back and look at what's happened to the ACNP and the field of psychopharmacology during the time you were at NIMH.

JL: There had been, from the beginning, a very synergistic relationship between the NIMH and the PSC about the creation of the American College of Neuropsychopharmacology and the International College. I think that it was the leadership of NIMH, and specifically Jonathan Cole's leadership, that brought that about. There was funding made available for supporting these meetings; there was encouragement for people to attend them, and there was a Government Industry Liaison Committee set up where people from the government told us what was going on and informed the ACNP and its membership what was happening. I remember coming to San Juan, to my first ACNP meeting, encouraged by Jonathan and I was awestruck by the number of research scientists participating and the breadth of what was going on. Then, year after year, I saw the progress made and was able to take the experience from interacting with people here back to my role at the NIMH. I could identify what gaps there were, and get the branch to try and see if we could fund work that needed to be done but wasn't. There was a study you probably remember well; the hyperbaric oxygen study we funded is a perfect example of what I'm talking about. .

SG: It was important that the need for that study was identified within your agency. Questions had been raised about therapeutic claims which, if they were true, needed to be validated because the cost of the

intervention was extremely high and it would only be worthwhile if you could prove its value conclusively. That's a clear example where NIMH took the initiative to address a public health need and from that data the important decision was made that funds should not be assigned because hyperbaric oxygen was not an effective therapy. That kind of projects would be important to do now with managed care. Do you think that NIMH is geared to do that sort of thing again?

JL: I don't think with current resources that it's possible. But it would be important to do those kinds of projects. Going back to the hyperbaric oxygen study, it was Small and Jacobs from Buffalo, who claimed hyperbaric oxygen treatment was useful in reversing the effects of senility or organic deterioration in older patients. And there was only their one study in the field. At the Branch we identified the need to replicate their finding; if true it was a 'breakthrough' both in terms of treatment and understanding the mechanisms underlying cognitive decline. On the other hand, if false, too many people are being put through very expensive treatments for no reason. And, entrepreneurs were moving in very actively because the hyperbaric chambers they made were being underused.

SG: Or lying idle.

JL: It was not an easy study to do, because you had to set up a proper design with investigators knowledgeable about how to select an appropriate control group and a set of outcome measures which were reliable and valid. Al Raskin was the person at NIMH, who was gently urged by me to move into this field after he had made tremendous contributions in the area of depression and antidepressant therapy. It took him about a year and a half, gathering information and the relevant people, before we could even imagine doing a trial. During that time he met with many people at your institution at NYU, with the Rusk Institute, and with Tom Crook to develop some novel measures. All of that was brought together before a study could be mounted and supported by grants. I don't see, at this point, that there is support and staff time at the NIMH to have a year and a half just for planning such a study. This is an example of a study the field couldn't do on its own because of the need for getting the right people from so many areas. Morris Lipton, the Professor of Psychiatry at Chapel Hill in North Carolina, used to say that the Psychopharmacology Branch was the Yellow Pages of Psychopharmacology. By that he meant we knew what was going on and who was doing what in the field, and could broker things to bring people together who ordinarily wouldn't collaborate on a project.

SG: This story is illustrative of what we are losing. I wonder if we could have some other issue you saw during your tenure you would like to comment on.

JL: I would like to go back to something that doesn't reflect so much on the current structure, but on how the field has changed. In the early days of psychopharmacology, and I'm referring to the 1960's, there were few investigators and not many standards; Psychiatrists didn't know about clinical trials and methodology. They knew about patients and how to try treatments. Psychoanalysts were prevalent, and looked at people who were trying to introduce medications as some sort of weird and far out group. Since the Food and Drug Administration had no efficacy requirements to market drugs before 1962 and because of "doubting Thomases" in the psychiatric and psychology professions that a drug could improve abnormal behavior, we had to prove to our colleagues that, in fact, medications could make a difference. So we set out to do controlled clinical trials which gave incontrovertible evidence these medications were working and proving that to our colleagues as well as to the regulatory agencies. So, because of the staff at NIMH and cooperation with the field, a set of standards was developed to be employed by a program called the ECDEU, Early Clinical Drug Evaluation Units, in which funding was given to about 18 centers around the United States to carry out clinical trials. People from those centers gathered together once or twice a year to exchange results with compounds they were testing. Early on, we realized that since different people were using different outcome measures and rating scales it was very hard to compare results from Bellevue in New York to results from Oklahoma City, for example. When this problem was identified, the NIMH and the investigators set up a standard battery, a cafeteria of scales, which could be jointly used as a set of forms, sent to the Biometric Laboratory, George Washington University, analyzed and returned to the investigators. The NIMH did not dictate the design of trials or which of the forms should be used. It did identify some necessary data, like the demographic forms and dosage records that were to be completed in all clinical trials. And, this was a very nice model and soon we started seeing, at meetings and other places, pieces of the output from the Biometric Laboratory appearing on slides. Not so slowly but surely, the field adopted these standards, and now there's no question the industry requires that kind of standard to be used in clinical trials. Something that was experimental, back in the 1960s has become standard in the field.

SG: You provided a method for very early evaluation of new therapeutic entities with small sample sizes. The system was so well organized and

had a cross checking system, so if Investigator "A" studied drug "B" and two other investigators also did drug "B", you could know very quickly whether there was consensus or not. You were able to get data very early with very small samples. Secondly, it provided a mechanism to investigate drugs without support by pharmaceutical companies. The NIMH would provide support for an investigator to study a product for therapeutic activity if he felt it was justified. Do you think a system should be a place again that would support studies like the hyperbaric oxygen chamber project?

JL: I think we've passed that stage. By now certain standards have been accepted and it's easier for companies to have their drugs studied. But if the funding could be put into some kind of pool, where people would be able to study what seemed to be the most interesting, we might see more worthwhile projects. Right now, I would go to the other end of the spectrum; we need studies of effectiveness. We still need studies of efficacy under ideal circumstances, but we also need studies in the field of routine practice, to see how well the drugs works in real life situations and we also need studies to see how one drug compares to another. The FDA standard for marketing is active drug versus placebo, so if you can show your drug is better than placebo in a defined diagnostic entity and is safe, your drug can be marketed. From the point of view of a clinician and patient, what we want to know is what would be the best or leading treatment for a particular condition from the existing drugs available. Unfortunately we don't have the scientific data to get that information, but that could be done with effectiveness studies. Now we don't have the methodology for effectiveness studies, although, over the years, we developed the methodology for doing efficacy and controlled clinical trials. I would very much like to see the NIMH push to create effectiveness studies to give us information that could be used for clinical guidelines. Guidelines are accepted by managed care companies, but we have very little scientific data to back them up or to know whether patients wind up being treated better. They may only lead to patients being treated cheaper.

SG: Thank you very much. I hope other people can learn from the questions we've raised and the issues that should be addressed.

JL: Thanks, Sam.

JEFFREY A. LIEBERMAN

Interviewed by Shitij Kapur
Scottsdale, Arizona, December 9, 2008

SK: My name is Shitij Kapur. I'm a psychiatrist, a member of the ACNP and I'm the Vice Dean of Research at the Institute of Psychiatry in London UK. It's my pleasure today to interview Professor Jeffrey Lieberman,* Lawrence Kolb Professor of Psychiatry and the Chairman of the Department of Psychiatry at Columbia for ACNP's archives. Professor Lieberman is also the Director of the Lieber Center for Schizophrenia Research, in addition to being the Director of the New York State Psychiatric Institute and the Psychiatrist-in- Chief of the Columbia University Medical Center of the New York Presbyterian Hospital. Professor Lieberman is undoubtedly one of our most prominent psychiatrists and scientists and it's my pleasure to interview you today.

JL: Thanks, Shitij. It's a pleasure to be here.

SK: Now Jeff we'll go through in a sort of chronological order of your life, and we'll start with where it all began, so where were you born?

JL: I'm originally from Cleveland, Ohio, and I was born and raised there. Then, I went off to college at Miami University in southern Ohio, as opposed to the University of Miami in south Florida and then came east to medical school at George Washington University School of Medicine. After graduating I went to New York for my training where I was a resident at New York Medical College Saint Vincent's Hospital and, then, moved on for research training at the Albert Einstein College of Medicine and the Bronx Psychiatric Center.

SK: How many states had you already done by that time? It seems you were in quite a few of them.

JL: Well, I moved around, went from the Midwest to Washington, which I guess is the Mid Atlantic region of the United States and, then, to New York and I've been in New York, where I currently am ever since, except for a ten year period at the University of North Carolina.

SK: What drew you into medicine, in the first place?

JL: I always had an interest in medicine, because at the time I was growing up it was a respected and very attractive profession and it seemed to be a worthy profession to aspire to, and I always liked science. I was also intellectually curious so it was easy to develop an interest in medicine. What galvanized it and also tended to push me in the direction of the neurosciences was that in the period I was in college, in the 1960's and

* Jeffrey A. Lieberman was born in Cleveland, Ohio in 1948.

the early 1970's, there was a great cultural ferment and pharmacologic experimentation that led to changes in ideas in terms of various chemicals being able to change the state of the mind. I remember taking a course in the Biochemistry of the Brain, and becoming fascinated to think that the thoughts and feelings people had were reducible to electrical charges and chemical molecules, and you could do experiments which would change the behavior of animals and humans. And then, came, the introduction of hallucinogens with the discovery of LSD. It was an incredibly dramatic experience to observe that a microgram, a minute quantity could profoundly alter someone's mental state, which then dissipated and the individual reverted to what had been their normal state.

SK: You said that you only observed these experiences.

JL: That's right.

SK: That's for the record! I have to get it right.

JL: Like our former president, I never inhaled.

SK: Did you do any research while in college?

JL: In graduate school, I was taking the typical Arts and Science curriculum with a major in Biological Sciences, so I did a variety of experiments in the laboratory and that was reinforcing in terms of what I had been thinking about beforehand. I was excited by the idea of studying human biology and physiology and to be able to do experiments to manipulate these variables to a desired outcome.

SK: As you went into medical school did you know that you were going to be psychiatrist?

JL: I was sort of inclined towards that, but I hadn't made a decision by any means. I wasn't somebody who said I want to grow up to be a psychiatrist. I went through the typical paths of doing the first years in basic science and the third year clinical clerkships where you rotate through all the medical disciplines. I went through the usual process of, when I was in OB/GYN, I felt that would be an interesting field to go into, and when I was in surgery, I thought surgery is really exciting, but psychiatry really resonated with what was previously my inclination.

SK: I don't know exactly how things were in your medical school, but it would be a reasonable guess that psychiatry in medical school at that point in time was not biological, or was it?

JL: No, it wasn't.

SK: So, how did you find psychiatry attractive?

JL: I was very intrigued by the things people were getting interested into with regard to psychoanalysis, group therapy, family therapy, the whole multi-generational family therapy and family systems of Gregory

Bateson, Jay Haley and people like that, which were prevalent at that time. Still, the greatest interest to me was the brain and how it could give rise to mind, personality and behavior. When I was doing rotations in psychotherapy, group therapy and the like, I was also taking electives at the NIMH, which I could do because I was in Washington, DC.

SK: So you did electives at NIMH while a medical student?

JL: I had an elective with Professor Roscoe Brady, a famous neurochemist, and made discoveries in collagen storage diseases. This was a rigorous exposure to the application of neurochemistry to brain and mental functions. In the early days of the NIMH, when it was still located on Wisconsin Avenue, as opposed to Bethesda or Rockville, I did some electives with a couple of people there.

SK: Was that critical in your decision to go into psychiatry?

JL: It was during my fourth year that I was doing electives, so by that time I'd decided.

SK: The electives gave you a glimpse of what psychiatry could be?

JL: Right, but even if I knew that I would go into psychiatry I still wasn't sure that I was going to pursue an academic career.

SK: So where did you take your residency?

JL: At New York Medical College, Saint Vincent's Hospital.

SK: How did you choose that program?

JL: I wanted to go either to New York or one of the West Coast cities, and Saint Vincent's was an interesting program, because it offered an eclectic curriculum. The training director was a protégé of Paul McHugh and was trained in the tradition of phenomenologists. It had an unusual orientation for a psychiatric program.

SK: Did you do a standard four year residency?

JL: Yes.

SK: When did your interest turn to academic psychiatry or neuropsychopharmacology?

JL: Probably late in the process. As you know residency in your first year is a blur. You're rotating through all the different services and take call at night. In the second year you do inpatient service, so you're admitting and taking care of numerous people with all the different manifestations of the major psychiatric disorders. The third year was mostly outpatient psychiatry, child and adult psychiatry with some consultation liaison. And, then, in the fourth year, I began to do electives, and the elective I did was research, psychopharmacologic trials.

SK: What was the first clinical trial you found yourself doing?

JL: The first trial was with an antipsychotic drug that's still available, but little used, called loxapine. It was a Phase II study. But what really

sparked my interest was reading journals like the American Journal of Psychiatry and the Archives that were more scientific and biological. This was now the late 1970's, and psychopharmacology was coming to fruition. There were two studies that crystallized my interest. One was done by Sam Gershon and Baron Shopsin, who were at NYU at the time, trying to determine the basis of the therapeutic effects of antidepressants. They treated acutely depressed people with antidepressants and then introduced parachlorophenylalanine or α-methylparatyrosine to inhibit the synthesis of serotonin or norepinephrine. They found that PCPA reversed the therapeutic effect of antidepressants.

SK: And AMPT did not.

JL: AMPT did not and so it seemed that serotonin was the critical neurotransmitter.

SK: So you were clearly intrigued by the end of your residency. But what did the average smart young psychiatrist graduating from New York want to do in those years?

JL: They were doing analytic training and they were getting trained in general psychiatry, likely with the intention to go into clinical practice. It was probably a minority considering an academic career.

SK: What would academic careers in those days look like? So, if you were a resident finishing residency what were the options available?

JL: The majority went into practice, because the healthcare financing system was not yet fully dysfunctional and reimbursement was reasonably good.

SK: If you wanted to move into an academic career, were there any options? Did you have to do a post-doctoral fellowship?

JL: Most people would do a clinical fellowship to have sub-specialty training in a particular area like child psychiatry, consultation liaison, geriatric, administrative, and then seek to be affiliated with a medical school, a teaching hospital, to run a unit, or a clinic, or direct a training program.

SK: What we would consider today clinical faculty?

JL: Right.

SK: Those who wanted to be clinician scientists, were there tracks available or did they have to create one for themselves?

JL: Well, tracks were in evolution; the scientific workforce in psychiatry was just taking shape. Post World War II, the NIMH was created and all of the scientific training in psychiatry took place at the NIMH. Graduates who wanted to pursue a scientific career needed to go to there for training. By the 1970's there had been an effort to broaden the base of training to academic departments, but, the NIMH intramural program was still the Mecca.

SK: What attracted you to follow that track, after you finished residency?
JL: I wasn't going to go to the NIMH, but I had no particular reason for not going.
SK: You just liked New York?
JL: Right, it was basically a matter of how to pursue training through a Fellowship and Columbia was a great program at the time. Cornell was still very analytic. At Mount Sinai, Marvin Stein, had just taken the Chair and was changing the emphasis from very psychoanalytic to something which was more eclectic. Albert Einstein was really one of the leading programs in the country at the time.
SK: Who was the head of that program?
JL: The head of the program in 1980 had been Edward Sachar, a pioneer in leading this revolution in psychiatry. He was introducing what is now the forerunner of modern neuroscience. Sachar was trained in neuroendocrinology and studied hypothalamic pituitary axis mechanisms and their regulation by neurotransmitters.
SK: That was all the rage in those days.
JL: Exactly. He was the Chair at Einstein. In the 1960's and 1970's it was one of the leading, if not the leading department in the country. Then, in 1978, Sachar took the Chair at Columbia. So, by the time I got to Bronx, Wagner Bridger was the acting Chairman and Wagner was a credible guy. He had been trained and was scientifically active in basic neuroscience before it was even remotely fashionable for a psychiatrist to do so. He was one of a handful of people, along with Eric Kandel and Sol Snyder, who were doing bench laboratory research in psychiatry.
SK: Did you work with him?
JL: He was head of the department, but I was working at the Bronx Psychiatric Center, one of the affiliate facilities, doing psychopharmacology. The area that I was working in was psychopharmacolgy and schizophrenia, but the particular focus of interest in research was tardive dyskinesia (TD).
SK: This was a major problem at the time.
JL: It was a big problem with rising prevalence figures.
SK: What was your first rigorous research project in TD?
JL: Arnold Friedhoff at NYU, had developed a dopamine super-sensitivity hypothesis of TD. We knew from the work of Carlsson and Snyder that the mechanism of action of antipsychotic drugs was to bind to the dopamine-D_2 receptor and antagonize dopamine so that chronic administration produced an up-regulation in a series of adaptive physiologic events; it was this up-regulation that produced therapeutic effects. We also knew that through their effect on the dopamine-D_2 receptors in the

striatum and consequent changes these drugs produced extrapyramidal symptoms which gave rise in vulnerable people to TD. Friedhoff's theory was that if you stimulated these receptors to excessive dopaminergic activity you could down regulate them by a receptor modification strategy. The idea was to use L-DOPA, a precursor of dopamine, to achieve that.

SK: To use L-DOPA in people with schizophrenia?

JL: Yes.

SK: So, they were on an antipsychotic and L-DOPA was added.

JL: Right, and he demonstrated you could down regulate dopamine-D_2 receptors with L-DOPA administration in rodents, pretreated and concurrently treated, with a D_2 antagonist. So, we did that study.

SK: What were the findings?

JL: It worked to some degree but there was tremendous exacerbation of schizophrenia, as one might expect, because L-DOPA increased dopamine synthesis and release, in spite of concurrent treatment with neuroleptics that blocked D_2 receptors.

SK: So you moved into research on dopamine and schizophrenia?

JL: That's right, but before doing that we recognized that the use of L-DOPA wouldn't work, and decided to try a dopamine receptor stimulant, instead of a precursor. So we designed a study with bromocriptine in tardive dyskinesia in which we gave it concurrently with an antipsychotic drug, but it blocked the therapeutic effect. This demonstrated that, even if the hypothesis we tested was viable, it didn't really lead to a successful therapeutic strategy. So, I learned the hard way.

SK: In the first two forays one good study turned out to be negative.

JL: Exactly.

SK: But, you persisted. Now, just to get the chronology right, which years are we talking about?

JL: This was from 1979 to 1982.

SK: Were you a Fellow or junior faculty?

JL: I was a Fellow and then moved to become junior faculty.

SK: So you were junior faculty in 1982?

JL: Right. At that time dopamine was clearly identified in the pathophysiology of schizophrenia by the work of Carlsson, Snyder, Meltzer and Stahl. At the same time, there was ongoing work by John Davis, David Janowsky, and Bert Angrist with challenge tests to enhance the release of dopamine, predict treatment response and break schizophrenia into pathophysiological subtypes. Since we knew that neuroleptics were effective but produced tardive dyskinesia, there was an effort to

minimize human exposure to these substances by drug holidays, trying to determine who needed to remain on treatment indefinitely, who didn't or whose medication could be reduced to low doses. We designed a study, using methylphenidate, to determine who could be withdrawn safely from medication.

SK: So you tried to identify patients with schizophrenia who were stable, by using a methylphenidate challenge?

JL: We tried to do it by evaluating their behavioral response to the methylphenidate challenge. We found was that patients with a mild activation of psychotic symptoms that subsided by the end of the day, were the ones with a very high chance of relapse. They relapsed much quicker than those whose symptoms were not activated. .

SK: So, all of them relapsed after their medication was stopped?

JL: Right.

SK: So, it was a successful predictor?

JL: Yes.

SK: Are you still using the test?

JL: We don't use it any longer. But what we learned was that close to ninety percent of patients could remain off medicine for months, if not for years during a five-year period. The reason for doing that research was to find out whether one could avoid tardive dyskinesia by reducing cumulative exposure to medication. Then, in the 1990's, drugs with lower neurologic side effect liability came into use and the fear of cumulative exposure diminished. Tardive dyskinesia somehow seemed a much more ominous and serious side effect than diabetes and weight gain which the new drugs can produce.

SK: Did you do any further analysis of the findings with the methylphenidate challenge?

JL: In further analysis we found that the group in which people relapsed the fastest and in the highest proportion was the one with activation of symptoms to methylphenidate and tardive dyskinesia, followed by the people who had activation of symptoms but no tardive dyskinesia and, finally, by the group who had tardive dyskinesia but no activation of symptoms to methylphenidate. What the findings indicated was that dopamine super-sensitivity was a phenomenon present in both the patients with tardive dyskinesia and in the patients with activation of symptoms to methylphenidate.

SK: Where did these findings lead to?

JL: To an effort to study first episode patients prospectively. We began a study in the mid 1980's, in which we followed the natural history of the illness and studied its underlying pathophysiology by a pharmacological

challenge test and neuromaging techniques, first using CT scans and later serial MRIs.

SK: At this time you were still at Albert Einstein?

JL: I'd moved from Einstein to Hillside Hospital, so I was working at Hillside, and involved in studying expression of schizophrenia and underlying pathophsiology in the course of the illness.

SK: I would like you review your findings in those first episode studies from the mid 1980's to the mid 1990's. How did major findings from your groups and others, in those ten years, totally change our view about schizophrenia?

JL: When I was in training and still in the 1980's, therapeutic nihilism pervaded psychiatry about schizophrenia. Schizophrenia was the cancer of mental illness and you were doomed from the womb. We could suppress the symptoms of schizophrenia with neuroleptics, but ultimately the patient was going to degenerate and become disabled and there was not much you could do about it. So in the course of studying the first episode of a patient's illness what became apparent was that, at the beginning of the illness, these were not dilapidated, deteriorated people, but normal like their peers, and responsive to antipsychotic medication in much lower doses than usually thought. What also emerged was that the prognosis of individuals was linked to how long they're ill before they get their first treatment. So the likelihood of achieving recovery or remission was related to the active period of psychosis before they were treated. Richard Wyatt's seminal paper published in 1991, in Schizophrenia Bulletin, reviewed the whole body of research pertinent to this issue. The findings gave rise to the idea that psychosis was bad for the brain and you had to stop it in order to prevent damage. At the same time, longitudinal imaging studies demonstrated that structural changes may exist to some degree, but of lesser severity in first episode compared to chronic patients. Our findings corresponded with those of René Kahn and many others. There are amazingly consistent findings in more than a dozen methodologically rigorous prospective studies; there is some progression in gray matter volume reduction and ventricular subarachnoid space expansion that correlates with outcome. All findings indicate that if you get people early in treatment and minimize exposure to the disease, then morbidity can be limited.

SK: With hindsight all these findings look so evident and obvious, but at that point in time they were not. The findings highlight schizophrenia research in the early 1990's. By that time all the new, so called, atypical antipsychotic medications came in. How did you find yourself in the midst of that debate?

JL: As I mentioned, my interest in psychiatry was sparked by an interest in pharmacology and when the newer medications were introduced, beginning with clozapine, my question was what makes clozapine and the new drugs different from other antipsychotic drugs. Being at Hillside, I had the opportunity to work with clozapine when it came back into the investigative process. Even if not a breakthrough drug, clozapine represents an advance in our armamentarium of antipsychotics.

SK: So, at Hillside, you were at the heart of some of the major breakthroughs in pharmacotherapy in psychiatry. But, rightly and wrongly, you would become most closely associated with CATIE. So, how did CATIE come to be?

JL: CATIE came to be mainly by circumstances in which I was enveloped and not in any way by my own initiation.

SK: Okay, we should clarify that. So tell us about the ferment and the feelings that gave rise to the funding, leading to CATIE; what led you to put together the partnership that finally became CATIE?

JL: The antipsychotic drugs were a large group of medications, widely used but generally regarded to be pharmacologically the same. The first real advance came with the introduction of clozapine, a breakthrough because it was effective in people who were unresponsive to all the other treatments. And at the same time, clozapine had this terrible side effect, agranulocytosis. It also had cardiac and metabolic side effects which were, like tardive dyskinesia had been, a big concern. There was a tremendous effort to duplicate clozapine that lead to the introduction of numerous second generation drugs beginning with risperidone, olanzepine and quetiapine, through the decade of the 1990s with ziprasidone introduced in 2001 in the United States. These drugs were seen as clozapine like; they inherited clozapine's reputation and didn't have to prove it. They were thought to be better and safer and became widely utilized. Over ninety percent of all prescriptions were for these newer medications; the price tag was extraordinary. The cost of the antipsychotic drug market in the US was less than five hundred million dollars in 1990 and, by 2001, it was over ten billion dollars.

SK: Ten billion?

JL: Ten billion! So people were beginning to wonder whether these drugs were really better and if they were worth the additional cost.

SK: We should take a moment, to record for history, that the period from 1993, till when risperidone was introduced, seemed like a glorious period. There was a sense of optimism, a lot of it, perhaps, misbegotten, and advertising for antipsychotics took over the field in a big way.

It was quite a time for schizophrenia; from having been a forgotten illness to suddenly being the darling.

JL: That's right. It was a very compelling time in psychiatry, as if we had really become a scientific discipline. We were making progress. Here's the evidence. We've got these wonderful new drugs; on the depression side we had developed fluoxetine, Prozac, developed by Ray Fuller at Lilly. Now we had all the SSRI's.

SK: It was a compelling period for psychopharmacology.

JL: That's right, and we felt we were on the march to eradicate mental illness or, at least, alleviate symptoms with fewer side effects.

SK: It was on the cover of Time Magazine. It was everywhere.

JL: That's right.

SK: You're saying that by 2000, there was a beginning glimmer of doubt?

JL: The bloom was coming off the rose, because the outcomes that were expected were not being seen by clinicians in their patients. The costs of mental health care were not substantially diminished but the cost of medications had increased enormously. So the question was what's going? So the NIMH decided to do what a number of other Institutes within the NIH, mainly cardiovascular disease, cancer and neurology had done previously. This was to get into the new fashion of large, practical, clinical or pragmatic trials to address the real world effectiveness of treatment, as opposed to the more pristine and rarified efficacy seen in rigorous randomized controlled studies, done for drug regulation and approval. NIMH decided they were going to request studies to evaluate the effectiveness of antipsychotic drugs in schizophrenia and they put out an RFA to do it. I had moved to the University of North Carolina when I obtained the grant in the mid 1990s.

SK: So you had finished your tenure at Hillside and moved to be the Chair at North Carolina?

JL: The Vice-Chair for Research and the Director of the Mental Health Clinical Research Center.

SK: From there you led the CATIE initiative. When did it start?

JL: Applying for the contract and the application process began in 1998. The project was awarded in October 1999, and the contract began in January 2000.

SK: This was a substantial contract. It's a matter of public record, how large was it?

JL: There were two studies. For schizophrenia, on one hand, and for Alzheimer's disease with psychosis and agitation, on the other. It turned out to be sixty million dollars.

SK: That was probably the biggest contract ever.

JL: It was the biggest contract the NIMH had ever done.
SK: Tell us what it was like organizing something of this magnitude which hadn't ever been done in psychiatry?
JL: It was a little like mobilizing for war; recruiting a set of generals and officers to participate in the process, so there were a number of institutions involved. Duke, UNC, Yale, University of Southern California and the University of Rochester were the lead institutions. Then we recruited a network that totaled eighty sites, including both schizophrenia and Alzheimer's disease.
SK: Wow! And you had support from Quintiles.
JL: Yes. We partnered with a contract research organization to deal with study management.
SK: Which is an interesting example of a new kind of collaboration, because the size and scope was so large it couldn't have been done from academic auspices.
JL: That's exactly right. We had to make a decision about whether to create an academic CRO or to partner with one. Given the timeframe, and when you're under a contract, there are milestones and deliverables. So, since they were investing sixty million dollars, we realized we better not screw this up!
SK: You certainly didn't.
JL: We didn't screw it up, but we stirred things up!
SK: Let's get to that. So the results came out when, in 2005?
JL: 2005. We began the project in 2000, and the first year was designing it. The question they wanted us to answer was how the first generation and second generation drugs compare, are the new drugs better? At the time it seemed a foregone conclusion that the second generation drugs were better.
SK: I remember debates with the ACNP. People felt it was futile to do the study; that we know the second generation antipsychotics are better, so you're wasting your time.
JL: That's right, but the question should have been, how do the second generation drugs compare to each other, which is better or in which patient is one or another better. That was the second question. And the third question was what is the cost effectiveness of these treatments? So, the first year we designed the study but it wasn't just designing it; we had to vet it. It had to be presented to a whole series of stakeholder groups and the NIMH had to bless it. It ended up, to some degree, being a study designed by a committee. We began, in 2001, enrolling patients and we completed enrollment in 2004. We immediately locked the database, cleaned it and in near record time, within four months,

finished the analyses. We wrote the paper and submitted it and it was published in September 2005 in the New England Journal of Medicine.

SK: That was a landmark paper.

JL: It was favorably reviewed. We had to modify the paper in a substantial number of ways to satisfy the editors concerns and we had to tone down the discussion a bit, in terms of the interpretation. But, basically, it was very favorably reviewed and people saw this was something that had produced an extraordinary result.

SK: People can go to the paper and read the results. I recommend they do so and tell us how the results clash with their expectations. That may not be in any paper but it would be nice to record.

JL: When we designed the study, we felt we had to put the final nail in the coffin as to whether the second generation drugs were indeed superior. That was the expectation.

SK: Was that your expectation?

JL: Yes, we felt we would simply prove it, because previous studies had been methodologically limited or too small.

SK: They were small indeed. When you opened the data and saw your findings, what did you think?

JL: We said there's got to be something wrong here. So, we went back and checked everything over and over, repeatedly, because I've had the experience before of coming up with findings that were very unexpected and having to go back over and over to verify this was accurate. In one case, we almost got scooped, because findings from another group turned up. It took over a year and a half to satisfy ourselves that our findings were accurate before publishing. So we barely, by a couple of months, got our paper into print before the findings of this "other group" turned up. So we went back, and it became apparent there's never been a data set that I've been associated with that's been as consistent as this, because we had multiple variables and the study was so large. We had numerous variables in the outcome domains; sometimes you get an effect on a variable in one domain but not in the other, and frequently this is lost in the reporting. But in the case of this study, where there were multiple variables within a domain, they were all consistent. The effect was very consistent across all domains. So, in the course of doing this, we developed tremendous confidence in the validity of the data, which was very helpful because, once it was published, the criticism was withering.

SK: So tell me about the criticism. You published your findings and it was going absolutely against the grain. Drugs companies were unhappy. How did that feel?

JL: I started wearing a Kevlar vest under my shirt, but it wasn't a pleasant experience because obviously it provoked the criticism and disapproval of a lot of people.

SK: Some within the ACNP?

JL: Absolutely, it was hotly debated. Even some of our CATIE investigators criticized the results, even though they participated in the data collection. But the thing which was probably the most disconcerting was that the stakeholder groups were very unhappy with it. So you ask who are you doing research for; obviously for patients, right?

SK: What were they unhappy about?

JL: They thought our findings would lead insurance companies and third party payers to restrict choice and say, if these drugs are no different why should we pay for the newer drugs? Go back to the least expensive ones. They also said that mental health care had been shortchanged for so long and this was just another way to pull money out of it. No, I said, that's not the idea. The idea is we can save money on your pharmacy and you put it into case management, housing, supported employment, vocational rehabilitation, things of that sort.

SK: We're three years post CATIE and a number of other studies have come out. How do you think they have reflected on CATIE?

JL: Every study has been almost completely consistent with CATIE. Recently, make note we're talking here on December 9, 2008, just last week Lancet published a large meta-analysis, which again produced a set of results very consistent with CATIE. While we were doing the CATIE study from 2000 to 2004, in the UK Peter Jones and Shon Lewis were doing a couple of studies for the National Health Service and the results were identical. At the same time, the NIMH, because of the fact that there was an extreme increase of antipsychotic drug use in young people, funded us to do a study in adolescent psychosis, so we did a version of CATIE. It compared one of the first generation drugs to two of the most commonly used second generation drugs in kids twelve to eighteen. It was a one year study.

SK: What was the name of that study?

JL: The TEOSS study, Treatment of Early Onset Schizophrenia Spectrum Disorders. It was in first episode patients, so it was a different population than CATIE.

SK: Right. So, here we go from 1993 to 2005. We're all high on these drugs, metaphorically, and then the floor falls out from under it and it would be fair to say that the last three years have been down. One after another study has been coming, suggesting our initial enthusiasm was wrong.

JL: We got carried away with what we thought was our own progress, but there was less there than we realized. It was a bit of an emperor's clothes phenomenon. This is not to say these drugs are bad; they're not, so we have many more options. These drugs pharmacologically have some differences from the old ones, but they're not the tremendous breakthrough we thought they were. In retrospect, we have to say that, looking back at the fifty years in which these drugs have been developed and introduced, that the rate of advance, in terms of innovation within a drug class, has been fairly limited.

SK: That brings us to today; we're at the 47th meeting of the ACNP and if we walk out of this room and listen to the talks, there's not much going on in the treatment of psychosis anymore. But you hear a lot about genetics and cognition in schizophrenia. Where do you think we'll be with that?

JL: Well, I think there is a lot going on with the pharmacology. The problem is we have a lot of theories that lead to targets for developing new drugs, but getting the drugs is not an easy process, because it is something academic investigators and the large majority of the members of the ACNP cannot do themselves. We need to partner with the pharmaceutical and biotechnology industries, but we're caught up in a process of engaging with the private sector and dealing with regulatory agencies. This process is one which has become heavy going; it's not simply where does the science lead you, but how do you get a grant to do the study? It's working with the bureaucracy of a corporation that has fiduciary responsibilities to their shareholders and, then, you have the regulatory agencies as well.

SK: Fair enough, but drug companies have always been in it for the overall benefit of their shareholders and the government agencies have always regulated drugs. Where do you see us going in the next ten years? We're in 2008 now.

JL: I think of two areas. First, the sequencing of the genome, the explosion of knowledge and methodology to probe genetic mechanisms is going to be tremendously important. Identifying genes will enable us to do personalized medicine. Right now we treat people based on their diagnosis; we don't treat people based on who they are even though we know there's tremendous variation within a diagnostic category. We'll be able to genotype individuals to determine what the risk genes are for developing a disorder or what genetic characteristics would predetermine their therapeutic and adverse response to a particular treatment.

SK: In theory what you said is unimpeachable. It is the logical outcome of what we're doing. The question is, in what timeframe? How quickly will

a doctor in the clinic be using genetics to make meaningful decisions about care of the patient?

JL: It's happening in some disciplines already, in cardiovascular disease and oncology. In psychiatry I'd say it's going to be within our professional lifetimes and I would hope we would see it within a decade.

SK: Your prediction is that by 2018, in ten years, we will have good markers routinely used to guide treatment in psychiatry?

JL: Yes, and possibly earlier.

SK: Wonderful, so, what is the second?

JL: The genes will lead us to proteins that will be targets for new drug development. Until now, virtually all the drugs have been discovered by serendipity. I think we'll have rational drug development.

SK: One has to say that this hope for a rational psychopharmacology has been around almost for thirty years and has led to a lot of rational testing. Unfortunately, none has led to a significantly different drug. So what is your time frame for gene driven psychopharmacology?

JL: That will be faster, I think five years.

SK: But, even if we have a drug by that time will it get through for clinical use?

JL: No, not for clinical use. But for a gene leading to the synthesis of a drug that enters clinical development.

SK: So your prediction is that in fifteen years we would probably see drugs developed on the basis of genetics in psychiatry?

JL: Hopefully, we're both right and no one can accuse me of being overly optimistic. But there's good reason for optimism.

SK: There is very good reason for optimism. Now, how has the ACNP been a part of your career? When did you first join? What are the different roles you've played within the organization?

JL: ACNP has been a prominent, prestigious and influential organization in the field, not just for neuropsychopharmacology but neuroscience.

SK: In the world?

JL: In the United States and possibly the world. Anybody who aspires to a career in this field needs to become involved as soon as possible.

SK: When did you first come to the ACNP?

JL: I don't recall the year, but it was probably in the early 1980's.

SK: Who invited you?

JL: It must have been Friedhoff.

SK: Do you remember what you presented?

JL: I don't think I presented anything, I came as a guest.

SK: What was your experience?

JL: It was unbelievable, like being a kid in a toy store, having all this wonderful material and these icons parading around, the great people in psychiatry; Gerry Klerman, Sol Snyder, Joseph Schildkraut and George Winokur. Everybody came to that meeting, annually.

SK: Have you subsequently come annually?

JL: I've come every year, I haven't missed. I had data to present the next time and eventually I was elected to membership and became involved over the years on committees. I also served on the executive council.

SK: Between Thanksgiving and Christmas?

JL: The timing has been something of an issue, but I attended, nevertheless.

SK: What was the most memorable event at ACNP meetings?

JL: There's probably not a single one. They're characterized by a certain set of personalities and presentations. There's a topic or a series of studies that pervades and dominates each meeting.

SK: But is there a year or a meeting that stands out, maybe for personal reasons, not necessarily for the science?

JL: Well, Oakley Ray was a tremendous personality, larger than life, and he became synonymous with the ACNP. For ACNP's twenty-fifth anniversary he organized an event at the National Press Club where a group of senior members reminisced and told anecdotes. That was a very memorable event. The ACNP usually rotates between the Hilton Hotel in Puerto Rico and a West Coast location or Hawaii; I remember a meeting in Hawaii that was one of my most successful, in terms of having two panels, a study group and some posters. By the end I was completely exhausted and happy to go with my wife on vacation.

SK: We started on a personal note and it would be nice to close on one. We left off personally when you were a young resident who had just begun at Albert Einstein. Where in all of this did you get married, acquire a family and find time to do anything else?

JL: I got married in 1980. I was a Fellow at the time, and proceeded to have two children, both boys.

SK: Is your wife an academic or in this business?

JL: No, she worked in Spanish television for many years.

SK: In Spain or Spanish television in the US?

JL: In the United States. My wife is originally from Chile and began working in the early days of Spanish television networks in the United States. There were two at the time, Spanish International Network and Telemundo. Subsequently, she went into the art business and had an art gallery representing Latin America Archives. Our two boys are now grown up and graduated.

SK: What are they doing?

JL: My elder son is a lawyer. He graduated last year and has his first job with a law firm in New York City. My younger son graduated college and is working for a consulting company in Latin America.

SK: You can't convert them to neuropsychopharmacology, but your wife managed to get one of them to Latin America.

JL: This is my explanation, if not an excuse. When I applied to medical school, medicine was probably one of the most desired, if not the most desired profession. The difficulty of getting into medical school was considerable. Over the 1980s and the 1990s, when they were growing up, the boom in business and financial services changed the career goals of a couple of generations of students and there was a migration. So, if my kids didn't follow in my footsteps that may have been a reason.

SK: We tried to cover a lot, but perhaps we left out something important you would like to record?

JL: The ACNP has played an instrumental role in the formation of so many people's careers by providing a forum where they can be exposed to all the scientific information relevant to their career development. They also get to meet their peers at annual meetings and have an opportunity to interact with leaders in the field. ACNP has a tremendous history and tradition; it's one of the most important institutions in our field that needs to be preserved and sustained in a way that maintains its vital role.

SK: Well, we hope both of those will happen.

JL: Shitij, that was great. You were absolutely outstanding.

SK: Thank you; this flowed very nicely.

DOUGLAS M. McNAIR

Interviewed by Leo E. Hollister
Waikoloa, Hawaii, December 11, 1997

LH: We're in Hawaii at the 36th Annual Meeting of the American College of Neuropsychopharmacology. These are history task force recordings of people who have had an impact in the field and who have many connections with it. Today we're starting off with Doug McNair* who's been in the field as long as I can remember and probably longer, actually, and who's had a very illustrious career. Doug, you're a psychologist by training, aren't you?

DM: That's right.

LH: What impelled you to become a psychologist?

DM: When I was a teenager I started reading Freud and Karl Menninger, and decided I was going to be a psychiatrist, probably also from going to popular movies and what I would now call lay literature. So I went to the University of North Carolina intending to go to medical school until I was a junior in college. After two years of college I was drafted right after World War II, the day after VJ Day. When I returned to Chapel Hill the VA training program came along.

LH: When the VA was trying to increase the number of psychologists?

DM: Yes. At that time it was a four year program. I was majoring in psychology and liked it a lot, although my minor was chemistry, so I was still building up a lot of pre-med courses. Then I decided to switch and go into psychology instead. I applied for and was accepted into the University of North Carolina, Chapel Hill program. I stayed from 1948 until I got my PhD in 1954. The first job was at Woman's College of the University of North Carolina, what is now University of North Carolina, Greensboro. I started out working in the Greensboro Mental Health Clinic and teaching part-time at the University and then switched over.

LH: This was after you had your PhD?

DM: Yes.

LH: Were you under any obligation to stay with the VA at that time?

DM: Not post-PhD. We did two years of work in the VA hospital while we were in the training program.

LH: I see. But you had no obligation to do work at the VA after you got your PhD?

DM: Not at all. I worked a couple of years in the Psychology Department at UNC-Greensboro and during those years decided I wanted to do

* Douglas M. McNair was born in Rockingham, North Carolina in 1927. McNair died in 2008.

research. We had to teach four courses a semester and three of those were in educational psychology, which I did not like at all. I started looking around and the job that appealed to me most was with Maury Lorr in Washington, when he was running the Outpatient Psychiatric Research Laboratory, OPRL. When I went there we were doing mostly psychotherapy research. We did a big collaborative study to find out whether twice weekly psychotherapy offers any advantage to once a week, and once a week over every other week. Then drugs came along and the collaborative studies in chemotherapy started and our group at the VA in Washington began meeting with you. We finally did a study which included meprobamate and chlorpromazine as adjuncts to psychotherapy with outpatients. I think that was the first drug study I was involved in.

LH: By that time the In-patient Multi-dimensional Psychiatric Scale, the IMPS, had been developed, hadn't it?

DM: The IMPS had not, but the MSRPP, the Multi-dimensional Scale for Rating Psychiatric Patients, developed by Maury Lorr and Eli Rubinstein was. The IMPS was a successor of it. In everybody's opinion the IMPS was a big improvement over the MSRPP. The MSRPP pre-dated the IMPS, by about 5 or 6 years.

LH: I see. But, you were instrumental in the development of the IMPS?

DM: Yes. I think most of that work was done in the very late 1950s, in 1957, 1958, and 1959.

LH: It was the only multi-dimensional scale for psychiatric inpatients, wasn't it?

DM: You are right. It wasn't long after we had the IMPS that John Overall and you developed the BPRS.

LH: Yes, Overall and Gorham took the IMPS and streamlined it, covering the same domains.

DM: Yes, I think the BPRS has the same 10 factors of psychosis as the IMPS. Lorr, Klett, Jack Lasky and I were the authors of the first version of the IMPS. I believe it was in that order. It was widely used in research at that time. Then we moved out of research in psychotherapy and exclusively into out-patient psychopharmacology. The first study was with meprobamate and the drug did not have any particular benefit, but we had some evidence combining chlorpromazine with psychotherapy offers advantages. As we got into that research we started to see more and more need for measuring instruments. There had been the IMPS for in-patients, but we needed psychometrics for out-patients, too. So, we started developing "feeling and attitude" as well as symptom rating scales very much like the SCL-90 or Hopkins Symptom Checklist. The

origin of the SCL-90 could be traced back to Adolph Meyer at Hopkins. The aim of these scales has been to have systematic ratings on how people felt. We were involved in the shaping of these scales and we got started on one of my main projects, the development of the Psychiatric Out-Patient Mood Scales or POMS. We kept the same acronym for the plainer version once we realized it was much more broadly useful and utilized than just in psychiatric patients. I'm involved right now in trying to update the manual and the bibliography. After I retired from Boston University, in 1991, I did the first survey of the literature for articles in which reference was made to the POMS, and there were more than 2,000 articles. In the last five years, there have been another 500 or so. It's used in almost every branch of medicine except radiology.

LH: Those were the first series of psychiatric rating scales, weren't they?

DM: They were.

LH: I don't remember any before the war.

DM: There was a predecessor to the MSRPP, developed by a priest at a Catholic University. I think his name was Father Brown, but I'm not sure; he developed a rating scale that Maury Lorr had a lot of respect for. I think he borrowed from it in developing these other scales. But you're right, there was very, very little.

LH: Now it seems there's a scale for every ailment, the business is thriving. I haven't seen Maury Lorr in years. What's happened to him?

DM: I talked to him this summer. Right about now he may be back from a trip over to Vietnam. He's in his 80's, and still moving around pretty well. He's Emeritus at Catholic University in Washington and still maintains an office there. He's pretty active.

LH: That's great! I remember when we started the VA Cooperative Studies Program that you were part of the group we put together. As I recall, we used the IMPS for the first two or three studies.

DM: Yes it was very sensitive in picking up drug effects.

LH: Those were the old days!

DM: It picked up not only the difference between drugs and placebo, but also between drug comparisons.

LH: That was amazing it could not only tell the drug placebo differences, but also the differences between drugs like chlorpromazine and mepazine, which at that time was thought to be a useful antipsychotic. It had some effect but not nearly as much as chlorpromazine. So, that was quite an achievement.

DM: Around the late 1950s, every year we had a VA Collaborative Studies meeting we would go from Cincinnati to Kansas City or from Kansas to Cincinnati , and I remember those meetings very fondly. You had

a big part in those studies and I always looked forward to your stellar presentations.

LH: Who was Chief of Psychology at the VA during that period of time?

DM: Max Houchins for most of the time and he was assisted by Cecil Peck.

LH: Cecil Peck was the one I remember.

DM: We used to have poker games after the meetings in the evenings.

LH: Could you say something about the research discussed in those meetings?

DM: The research was more and more in the outpatient area as we got involved in more drug studies. Every study in psychopharmacology I was involved in, included psychotherapy as a component. In the early days we were involved with all kinds of drugs, but later on, we moved more to studies of antidepressants in outpatients. While I was in Washington Maury and I did some of the early work with Librium (chlordiazepoxide).

LH: That would have been around 1959?

DM: Yes. Librium was succeeded by Valium (diazepam), and we did one of the early outpatient studies of Valium. Benzodiazepines, appeared to be considerably more effective than meprobamate, which was what we started out looking at, and produced fewer side effects in outpatients than chlorpromazine.

LH: In those days, most psychotherapy was still more or less analytically based, wasn't it?

DM: Yes, very much so.

LH: As compared to today's more tailored psychotherapies, which go after specific areas, they were largely rehabilitative.

DM: Yes, psychotherapy is more focused now, highlighted for specific disorders. Back then, DSM-II was in use for diagnosing and that was not a rigorous way of classifying patients.

LH: In DSM-II there was no disorder called schizophrenia; there was schizophrenic reaction, as though schizophrenia was still a reaction to interpersonal problems or problems of the environment, rather than an intrinsic illness.

DM: Not exactly the medical model.

LH: When did you move to Boston University?

DM: I worked with Lorr in Washington from late 1956 to mid 1964, and then moved to Boston University School of Medicine. In 1970 I became full Professor in Psychiatry with a joint appointment in the Psychology Department. In 1980 I became Director of Training in Clinical Psychology. They asked me to consider taking it; I would have never considered applying for the job because I was much too research orientated. But

it did work out and I became a token researcher. I moved my lab to the main campus of Boston University, on the other side of town from the medical campus.

LH: The medical campus is near the old City Hospital; whereas the main campus is across the Charles River from Harvard.

DM: Yes. I stayed another ten to twelve years until I retired in 1991. By that time, we were studying tricyclic antidepressants and focused on their possible effects on cognitive functions, working on the assumption the cholinergic system was related to memory and we found the anticholinergic properties of tricyclics varied a lot.

LH: Oh, yes.

DM: Amitriptyline was strongly anticholinergic, imipramine was in the middle and desipramine was fairly low. We were using measures of short and long term memory, semantic memory, psychomotor function, and attention.

LH: Were you using the drugs as tools for exploring hypotheses about memory, learning and things of that sort.

DM: Yes. We began to look at the effects on elderly people. The focus was on cognitive effects, but we were also looking at dose-effect relationships in normal elderly subjects who came in once a week for a few weeks while taking very low doses of tricyclics.

LH: Was this done in collaboration with the VA Unit studying aging, in Boston?

DM: No, it was something we were doing on our own. We were using doses of 5 or 10 milligrams of amitriptyline and the other two agents and found even such low doses had strong cognitive effects in people over 65.

LH: One of the paradoxes that has been true of these drugs is that most of the time in normal people they're obnoxious. Most of the antipsychotics, at least the older kind, and most of the tricyclics were very unpleasant for normal people. But the crazier or more depressed you were, the better you tolerated them.

DM: I've known you for about forty years; time goes by very fast.

LH: I've always been discouraged by the fact the VA collaborative studies with psychotropic drugs have never been given the credit they should; they pioneered a very advanced technique at the time to study drugs. Later on, several states emulated those studies, as did the Psychopharmacology Service Center at NIMH, but the VA studies were the first.

DM: They were the original studies so I have felt concerned about that, too. The Collaborative VA studies were clearly first. Nothing like that had

been done before, and the collaborative studies that followed were very much, "me too" studies.

LH: In retrospect I'd call those studies massive scientific overkill because, by that time, people who had any eyes and ears or powers of observation could tell these drugs were doing something vastly different from those we had before. But in those days, psychiatrists were still very much against the notion drugs would have an effect so we had to do that overkill.

DM: I suppose so. I think those studies had to be done. When I came into this field most people in medicine looked at psychiatry as anti-science and doing those studies pioneered development of clinical trial methodology far ahead of the rest of medicine. Some of the stuff today you read in other fields is amazingly naïve compared to the standard of clinical trials in psychiatry.

LH: Of course, the concept of controlled clinical trials didn't start with us; they were first used to test anti-tuberculosis drugs in 1945-46. Harry Gold at Cornell was talking about controlled blind studies way back in the 1940's. But I think our group advanced the cause more than any of the others.

DM: I agree.

LH: Earlier in this meeting there was a big session on how to study drugs in multi-clinic trials. It could have been the same damned thing we were talking about 40 years ago.

DM: I had told my wife I had seen that title over and over.

LH: It was exciting then because nobody knew for sure what the answers or proper procedures were.

DM: One great thing the ACNP did was provide the mechanism for all these people to come together.

LH: The ACNP has been a wonderful organization for cross fertilization between disciplines. I'm fearful we are going too much toward the neuroscience side and concerned for what a psychologist can get out of this years meeting.

DM: That concerns me, too. There are many papers where I can't even understand the title. But I've never spent time trying to predict the future, so I don't know where it's going.

LH: But you've never had any regrets about the course you took?

DM: No, I think I'm lucky. I've certainly had regrets about doing things I don't like, but they have been minor, compared to the fact I was able to do something I like and make a decent living doing it. I suppose if I had known how to make a living from statistics and quantification mathematics I might have considered doing that. Once I got into the field one

of the people who influenced me most was Ben Wiener, who wrote that famous book on experimental design. He was a professor at Chapel Hill when I was there and I got interested in analysis of variance because he showed what we could do with it. When I came to ACNP the first time it seemed clinical psychology was closer to being a good hard science than at present. There were a lot of people like Jim Klett, me, and John Overall with psychology training, who were into quantification.

LH: People I would call psychometricians, biostatisticians.

DM: Yes, I think we contributed something to the development of study designs.

LH: Yes, from the statistical point of view.

DM: But I don't think this is the place any longer for psychology. It bothers me there are not more people with the orientation and background we had coming into this organization. I believe they are not coming because they don't see their place in it any longer.

LH: That's been one of the great concerns among some of us that ACNP is getting imbalanced. I wonder who is going to replace the people you mentioned like Klett, Overall, you and several others. You retired in 1991?

DM: I became emeritus then.

LH: Lots of difference, isn't there?

DM: I get along because I have my computer at home and I can use the big computers at BU for data analysis. I find things like Medline on the internet just wonderful. In the year I retired, I got a contract with the Defense Department to evaluate a demonstration project for training psychologists to prescribe psychotropic drugs that's been going on for almost seven years. An ACNP committee of four psychiatrists and four psychologists constitutes the evaluation panel. We visit this training project several times a year.

LH: Is the program still on?

DM: They have stopped admitting new people, and there's no one in the formal training program right now. The program included one year of didactic medical school courses and one year intensive clinical work on the psychiatric ward at Walter Reed. Everybody has finished those stages and there are no new people admitted. There may be another contract to follow, but I'm not sure.

LH: There's always been a turf battle between psychologists and psychiatrists about psychotherapy and now we have another about prescribing drugs.

DM: I don't know what's going to happen. There is no consensus among members of the panel whether these people will ever reach the point

of independent practice in prescribing medications. Some of us think some will, but we have doubts about the medical safety. If you think these people have had two years of very intensive training after their post graduate work and they are still not ready to be turned loose as independent practitioners, I would say that , if you are a psychologist and want to prescribe drugs, you would be better off going to medical school.

LH: It almost becomes the equivalent in time anyway. What surprises me is that psychologists want to go into that field rather than pharmacists. In some state hospitals most of the prescribing is done by pharmacists and signed off by psychiatrists.

DM: Probably so.

LH: Where do you envision the place of psychologists will be in the ACNP, in the next ten years? We're both worried about the fact the role has diminished in the last ten years. Is it going to improve in the future?

DM: I honestly don't know. If the job needs to be done and the psychologists aren't there to do it, somebody else is going to pick it up. In the last 30 years or so, there has been a decline in the number of psychologists working with the field. Some psychiatrists have become extremely good at data analysis, so they may pick it up. Or they will hire people who are more real statisticians than psychologists ever were. I think it helps to know something about the field where the data come from that you're dealing with.

LH: The trend in psychology is toward the experimental or physiological approach, rather than the purely clinical, as it used to be. For instance, the other night I met a young woman, who's a psychologist and very much into brain imaging techniques. That's something 15 or 20 years ago, none of us could have foreseen.

DM: It's true that psychologists do everything under the sun. They practice in clinics, they are Deans in schools, and they're into MRI's and PET scans. Neuropsychologists I admire for their testing and measurement skills, especially in the area of memory and so on, but their statistical sophistication has been lacking. There is no reason this couldn't improve; I don't think we'll ever reach a time when we don't need to measure.

LH: A few years ago I did a pilot study with a neuropsychologist in our hospital; he compared findings with brain scan and neuropsychological testing and the agreement wasn't very good.

DM: That's a real validity check.

LH: Is there anything you would like to see happen in the future?

DM: The two things I hope may happen, and these may be clichés, I would like to see something developed to control anger and violence. Maybe psychopharmacology will develop something that contributes to reducing violence.
LH: That would be quite an achievement.
DM: There are people working on it and maybe it will happen.
LH: Every time you turn on the television set there's a guy standing there with a gun or knife in the movies. Violence is so pervasive. Doesn't it make sense to think that must have some influence on the viewer?
DM: There is fairly solid evidence that if children are exposed their play is more violent.
LH: When I was a kid we used to play games of cowboys versus Indians.
DM: I did the same.
LH: If your cap pistol went off your "enemy" would drop like they were killed. But of course, we didn't connect to the fact somebody who fell to the ground was never going to get up. They were going to get up in the next two or three minutes and the game resumed.
DM: Playing dead!
LH: It's as if people are taking that juvenile approach and extending it to their thinking about adult life.
DM: There's violence between the ages fifteen to twenty-five and in Alzheimer's at the other end. It looks like there's some hope for drug research for Alzheimer's.
LH: The most encouraging part about Alzheimer's is if you keep using your brain you're likely to keep it; you are a good example of how to avoid Alzheimer's.
DM: I don't know about that. Sometimes my memory for names is not what it used to be.
LH: This business of remembering names is tough. Well, it's been nice talking to you, Doug.
DM: You were a role model for me in the early days, and I appreciate you asking me.
LH: The biggest thing I had sense enough to do was to know what I didn't know and get people who could teach me like John Overall, who has been my main mentor.
DM: You were one who really understood all this stuff.
LH: Thanks for having this interview and I hope you have many more years so we can interview you again.
DM: Twenty more years if I have something to say. That would be great. Thanks a lot, Leo.

JOHN E. OVERALL

Interviewed by Thomas A. Ban
New Orleans, Louisiana, May 9, 2001

TB: This will be an interview with John Overall* for the archives of the American College of Neuropsychopharmacology. We are in New Orleans at the Annual Meeting of the American Psychiatric Association in May 2001. I am Thomas Ban. I'd like you to begin by telling us who you are in more personal terms, where you were born, early influences on your life, education, and things like that.

JO: I can give you a brief overview from start to present.

TB: Please do.

JO: Looking backward in time, it might be considered I haven't traveled very far in my career. Born in Texas, educated in Texas public schools, baccalaureate degree from Trinity University. in San Antonio, two years military at Lackland Air Force Base in San Antonio, and a PhD. degree in General Experimental Psychology from University of Texas (UT) in Austin. During the last two years as a UT graduate student, I worked as research psychologist with the behavioral medicine group of the UT/USAF Radiobiological Laboratory at Balcones Research Center near Austin. From there, I took a combined five-year "sabbatical" away from Texas, which included a National Science Foundation postdoctoral fellowship in psychometrics and multivariate methodology at the L. L. Thurstone Psychometric Laboratory of the University of North Carolina in Chapel Hill, two years as Chief of Criterion Development for the Veterans Administration Central Neuropsychiatric Research Laboratory, and two years as Associate Professor of Psychology at Kansas State University where I was also recipient of an NIMH Research Career Development Award. I returned to Texas in 1963 as Director of the Research Computation Center of the University of Texas Medical Branch in Galveston and Associate Professor in what was then the combined Department of Neurology and Psychiatry. I was promoted to Professor with tenure in 1967 and transferred at the same rank and title to the Department of Psychiatry and Behavioral Science of UT Houston Medical School in 1978, where I remain to date.

TB: Where were you born in Texas?

JO: In Gonzales, Texas, approximately two weeks before Black Friday in 1929. My father was a small-town lawyer in Gonzales, and my earliest memories are associated with growing up in the Depression years.

---

* John E. Overall was born in Gonzales, Texas in 1929.

From the point of view of my family, the Depression extended and got worse for several years as people exhausted their resources. In 1933 though about 1935, things were at their worst, so my family didn't have a whole lot of money when I was a child. My father occasionally took livestock and other produce for fees. Once he took a small herd of Spanish goats. He had them butchered and put the wrapped packages in a cold storage locker at the local ice house, which was what people did before home freezers came along. We ate a lot of goat chops, ribs, and sausage that year. Everyone had a hard time in those years and jobs were scarce. In spite of the shortage of cash, my mother was able to have a maid who was a combination of housekeeper and cook, and who looked after me while my mother taught school to supplement family income. My maternal grandfather came to live with us, and he also devoted a lot of time to me. I started school in Gonzales at the same elementary school where my mother was teaching. Things continued to be bad during those years, and my father's law practice suffered a dramatic setback when the older lawyer, with whom my father worked, died. Soon after that, my father gave up and moved the family to San Antonio where I entered the third grade.

TB: So you grew up in the Depression years and the death of your father's law partner had a significant effect on your life?

JO: My father had gone to Gonzales after graduating from law school to work with a successful older lawyer, the one who died. They shared the second floor of a building on the town square across from the courthouse. Things went well initially, but coincident with the Depression getting worse, the wife of the older lawyer died. As the story goes, the older man drank himself to death over the next year while remaining night and day closed in his office. How much the Depression had to do with that is questionable, but it had a lot of consequences for my father and affected me in a big way as well. Soon after the death of his mentor, my father reached a decision to accept a position as associate to a prominent lawyer in San Antonio who had a suite of offices on an upper level of the Smith Young Tower, which was the only "sky-scraper" in downtown San Antonio. The home in Gonzales was sold for whatever it would bring in the Depression. A moving van came, and the family was loaded into the car, together with personal belongings and a pet canary, for the trip to San Antonio. But at Luling, Texas, only about 35 miles from Gonzales, an oil company flatbed truck made a sudden left turn in front of our moving car, and an accident that totaled our car was unavoidable. While my father was arranging for transportation on to San Antonio, he called the office of the senior lawyer with whom he

planned to work in San Antonio and learned that the lawyer with whom he planned to work had committed suicide by jumping out of his upper-floor office window. Now my father had lost a second senior partner whose guidance he had counted on to launch a long-term career. We arrived in San Antonio with little money, no car, no house, and no office or associates to help in getting established. Those events helped place the move to San Antonio in context of the Depression more than any other in my memory.

TB: Now tell me more about your life after the move to San Antonio.

JO: I don't remember much about the remainder of my elementary school years. I recall getting into a fist fight when trying to stop a bully picking on my friends. I had never been in a real fight, and I thought I was getting the heck beat out of me. I went home a loser, even though it was mostly my pride that took the beating. I didn't have a mark on me, and my parents insisted I get up and go to school the next morning. I felt a lot better when the bully showed up with a big blue shiner. I learned two lessons from that which have remained with me to this day.

The Second World War came about the time I was entering junior high school. That ended the Great Depression, but didn't end its effects on my life. Early into the war, when most of the older boys were going into the service, I managed to pick up more home-delivery newspaper routes and delivered more newspapers than anyone else in San Antonio. That presented a problem for my attempt to fit into the teenage social culture of a mostly upper middle-class high school environment. Students in the San Antonio school system were stratified into high, middle, and lower ability groups, but that tended to represent social stratification as well. I was put into a high ability class, but the correlation ended there. My father was still struggling to get his solo law practice going without any help and the family had no money to spare. I entered teen years feeling a need to begin taking care of myself. It wasn't so bad. I made a lot of money for a teenager with my multiple paper routes. I had a car of my own, a liberal gasoline ration card because of my newspaper delivery work, and on numerous days in the fall and winter I got up in the wee hours to finish my morning paper routes in time to go duck hunting by dawn at a lake south of town. A friend named Richard Culpepper and I worked in the summers at an exclusive hunting club on the lake. We constructed deep-water blinds and nailed new palm-branch camouflage to others, replaced anchor lines, and painted the heavy wooden decoys for that day to look like bluebills, pintails or mallards. For that work, we two teenagers were granted full membership privileges, including breakfast at the club

house and participation with the men in drawing bingo chips from a hat, which determined where each member was to hunt. Certain locations were better than others, depending on the wind and weather, but that didn't matter to my friend and me because we usually hunted the shoreline. I'm amazed at the energy I had in those days.

TB: Did you graduate from high school in San Antonio?

JO: I didn't, although I was beginning to integrate into the environment of a socially-stratified high school. In spite of my divergent interests, I joined a high school fraternity and was beginning to feel at home in San Antonio. But another big change occurred when my father retired in 1946. His retirement, while I was still in high school, had a major impact, not only on my education, but for later life as well. I was 17 and a senior in one of the two large public high schools in San Antonio. My father had been working for much of the time to untangle the interests of 16 heirs to a country estate in which my mother owned a share. Working with the surviving heirs, one at a time, he cleared the title to the property by buying out or arranging financing with each of them. We then moved to that country place near a town named Round Rock in central Texas, about 20 miles north of Austin. My father always wanted to live in the country like he did when growing up. Round Rock is now a large suburb of Austin where the Dell Computer factory is located, but in 1946 it was quite small. My graduating class at the Round Rock High School had something like thirty-five students in it, and that was a disappointment for a big-city boy from San Antonio. A mitigating factor was I made the football team and set track-and-field sports records in the smaller league. From there, I went to the University of Texas at Austin and stayed as long as I could with the Korean Conflict going on. When I was bussed to San Antonio for a draft physical, I decided it was time to volunteer for the Air Force.

TB: Tell us about your life at the University of Texas in Austin before you joined the Air Force. You went there right out of high school?

JO: No, I skipped a step in telling about my undergraduate college days. I actually started college at Texas A&I in Kingsville, Texas. My parents were afraid I wasn't ready for the big time. It was the best educational choice I could have made. I did well in the curriculum there, got a good start by putting basic freshman college courses behind me, and was ready to transfer to the University of Texas in Austin after completing my freshman year. But I still wasn't ready to get serious about my education and where I was going after that. It took another important move to get serious. That came when going into the Air Force interrupted my tenure as a perennial undergraduate at the University in Austin. I

had gone there for five years in addition to the year at Texas A&I. After six years without receiving a degree, I was about to be drafted and volunteered for the Air Force. I was a late bloomer, and didn't apply myself to study in my undergraduate days. That is why, when I try to recollect my undergraduate education, it is the other things I did that are most prominent in my memory. My slower pace at the University allowed me to support myself by working part-time during the school year and throughout each summer. I didn't attend summer sessions in college. Instead, I worked at a variety of jobs to help support myself and because I wanted to. I boast I held more part and full-time jobs for meaningful periods than anyone I have known in my subsequent life. I never wanted to be just a nerd or just a college professor either. I started working at age 14 and kept it up. That allowed me a range of experiences in the real world I treasure. I single-handedly hauled in tons of bailed hay the summer after we moved to the country and hefted it up to the rafters of a two-story barn at the family's new country place. That was viewed as keeping in shape. Subsequently, I measured cotton acreage for the Department of Agriculture one summer and worked at a cattle auction barn part-time during one school year. Apart from my agriculture-related pursuits, I worked as deck hand on a shrimp boat on the Texas gulf coast, a travel information agent on the Mexican border, in a canning factory, sold insurance, worked as a collection agent for a loan company and worked on a railroad gang. Those were just a few of the thing I did while in school.

TB: You mentioned you were in the Air Force. Tell us about your military career.

JO: I didn't do the most heroic thing when my college draft deferment was running out. I decided to volunteer for the Air Force. At the same time, I was very much in love with my wife-to-be and didn't want to risk going off and leaving her. We got engaged before I took off for the Air Force. I made up my mind I would stay at one of the several air bases in San Antonio. I didn't realize people don't just "make up their minds" in the military, but it happened to work out for me. I went through basic training at Lackland Air Force Base in San Antonio and stayed there the whole time I was in the Air Force. I went through a couple of Air Force schools, into an Academic Instructor's Squadron, and then on to Officer Candidate School. About the time I received my commission, President Eisenhower was elected, and decided to cut back the military. I was offered the opportunity to be discharged into the indefinite active reserve, and I took it. The Air Force made three important contributions to my educational progress. I had not received a baccalaureate degree

before leaving the University for the Air Force but Lackland Air Force Base was home to the largest concentration of psychologists ever assembled in what was called Personnel Laboratory, which had the primary mission of developing measurement instruments for pilot selection. Many people in that endeavor were young academic psychologists who wanted a teaching career but were there to fulfill their military obligation, as I was. Trinity University of San Antonio took advantage of this to open a program of night classes on the base, employing some of the young psychologists who wanted to teach. I took courses and that, plus completing a couple of courses on campus in town, resulted in my finally receiving a BS degree from Trinity University in San Antonio, rather than from the University in Austin. It is also how I ended up in psychology rather than one of the other areas I had tried majoring in before I left the University of Texas. The third benefit provided by my Air Force experience was it gave me time to grow up. I got married and became serious about making something of my life.

TB: Was this in the early 1950s?

JO: That was in 1954. I left the Air Force, active duty at least, and went back to the University of Texas in Austin for graduate school, where I completed work on my PhD in 1958. As a graduate student, I worked at the Radiobiological Laboratory of the University of Texas and the US Air Force on an Air Force contract. I didn't personally train the monkey, but that was where Sam, the "space monkey", trained to become the first primate in space. The broader mission of the Radiobiological Laboratory was to examine the effects of head and whole-body radiation on learning, memory, and performance. It was anticipated that atomic-powered aircraft would soon become a reality, and there was concern about the effects of radiation on pilots. Rhesus monkeys were our primary subjects for the memory and decision- making studies, and rats were used for studying the biological effects of radiation on activity level, endurance, and other kinds of physical performance radiation exposure might affect.

TB: Weren't you involved in conditioning research in those years?

JO: That is how I got to the Radiobiological Laboratory, but wasn't what I ended up doing most of the time. They used various kinds of conditioning tasks for the monkeys in order to observe their performance on learning, memory retention, and discrimination tasks and see how head or full-body radiation affected those abilities in the short and longer term. A famous test instrument used for these studies was the Wisconsin General Test Apparatus. A monkey was placed in a small cage with a closed door separating it from a tray with stimulus objects

on it. When the door was raised, the monkey received a token food reward for choosing the correct stimulus object. Ironically, the monkeys performed better after radiation. I think it must have been because they were less distractible and didn't nervously turn round-and-round in the cage, like impatient monkeys are prone to do. The radiated monkeys just sat there and paid attention to the task. Although improvement in performance was certainly not what was expected and might have been a hard sell as an effect of radiation, psychologists made the most of it and produced a series of papers elucidating a new "theory of distractibility". My work there is when I first concentrated on statistics. My primary role at the Radiobiological Laboratory became analysis of the data using a Frieden desk calculator. The calculator the Air Force contract bought was top-of-the-line, called a "square root Frieden" because it had a built in capability to take the square root of any number, large or small. That was in addition to adding, subtracting, multiplying, and dividing. I turned out several reports to the Biomedical Research Support Center of the Air Force which was then located at Randolph Field, and I participated in or supported a number of publications in psychology and related journals reporting, and trying to explain, the "negative results" from studies in which radiation appeared to enhance performance. The work was also important for my being awarded a National Science Foundation postdoctoral fellowship after receiving my PhD.

TB: How did you get involved in statistics?

JO: My interest in statistical methodology was stimulated by my work as a graduate student at the Radiobiological Laboratory and by taking advanced courses in experimental design under a distinguished professor, Lyle V. Jones, who spent a year at the University in Austin while on sabbatical from the University of Chicago. He was an impressive scholar, and seemed to take an interest in me. He went back to the University of Chicago briefly before he moved to head up the Psychometric Laboratory at the University of North Carolina in Chapel Hill after the death of its founder L. L. Thurstone, the psychological measurement and multivariate statistics icon. Thurstone had himself moved there upon his retirement from the University of Chicago. As a consequence, I decided to take my NSF postdoctoral year in the Psychometric Laboratory at UNC after being invited and sponsored there by Lyle Jones. The Psychometric Laboratory provided a good environment for self-directed study and, separately, the Department of Statistics at the University of North Carolina at Chapel Hill also had a concentration of statistical expertise in multivariate methodology. The Statistics Department at UNC was a participant in the Research Triangle

Statistical Institute, which combined the talent from three different institutions. The Department of Statistics at UNC in Chapel Hill provided the primary theoretical and multivariate component, North Carolina State University at Raleigh was known for contributions in experimental design and applied statistics, and Duke University in Durham provided an educational focus. Most of the courses taught in the Department of Statistics at Chapel Hill were beyond my training as a graduate student. I nevertheless enjoyed the atmosphere the setting provided, and some of the outstanding scholars in the area of multivariate analysis occasionally came over to the Psychometric Laboratory to give scaled-down lectures for the trainees. I only realized later how much I absorbed.

TB: So, this is how you became involved in statistics?

JO: I did not know what I was going to do after my postdoctoral year. It was 1959 by then. I contemplated taking a temporary position in the Department of Psychology at UNC, but the only thing offered was a temporary teaching slot in Social Psychology. Then a real break came in the form of an invitation to join the staff of the Veterans Administration Central Neuropsychiatric Research Laboratory at Perry Point, Maryland. As an inducement, I was offered the title of Chief of Criterion Development. The move offered three advantages that provided an entirely new and lasting direction to my career. First, the Central NP Laboratory had the responsibility for design, monitoring and analyzing data from the large-scale controlled studies of chemotherapy in psychiatry pioneered by the VA soon after the arrival of chlorpromazine from France in the early 1950s. Unparalleled volumes of data descriptive of psychopathology from a broadly defined psychiatric patient population were arriving at the Central NP Research Laboratory on which I could apply my newly acquired multivariate statistical analysis methodology. As Chief of Criterion Development, I had access to a voluminous data base from which to distill the dimensions of manifest psychopathology that would lead to rating-scale quantification, the best known of which became the Brief Psychiatric Rating Scale (BPRS), which I authored in collaboration with Donald R. Gorham in 1962. The second major advantage was that it served as an arm of the VA Central Office in Washington. It was not administratively tied to the Perry Point VA Hospital, although it was located on the extended hospital grounds. The Central NP Research Laboratory had a separate Advisory Committee composed of senior VA clinical investigators from around the country who met at the VA Central Office in Washington, DC three or four times a year. My immediate boss, Julian J. Lasky, myself and two other psychologists from the Perry Point Laboratory were expected to attend the Advisory

Committee meetings. The Central Office support for the research coordinated by the Perry Point Laboratory also included sponsorship of an annual meeting for the larger number of VA doctors and others who voluntarily collected data for the early large-scale VA "Cooperative Studies of Chemotherapy in Psychiatry". That was important for me becoming acquainted with key people in clinical psychopharmacology research, the most important for my later career being Dr. Leo Hollister with whom I formed a long-term collaborative relationship that continued for more than two decades after I left VA employment. At the time I first met him, Leo was chairman of the Advisory Committee with which we met at the VA Central Office in Washington. Third, and most important for my contribution to assessment in clinical psychopharmacology research, was the almost simultaneous arrival at the Central NP Lab of Donald R. Gorham who partnered with me in the development and initial testing of the Brief Psychiatric Rating Scale. Don Gorham was an older seasoned clinical psychologist who was invaluable in providing clinical insight and rating-scale experience. He arrived with a reputation for development of the Gorham Proverbs Test, based on the importance of loss of abstract thinking ability among the earliest clinical signs of major mental illness. Another important lasting relationship that originated in the VA Central NP Research Laboratory was with C. James Klett, who arrived as Associate Director of the Perry Point lab two or three years before Don Gorham and I. Ten years later, Jim Klett, and his wife Shirley, spent a summer in Galveston working with me to finish up a book entitled *Applied Multivariate Analysis,* which Jim and I coauthored in 1972.

TB: It seems the laboratory had an impressive staff?

JO: I guess it did. The lab was already in possession of a tremendous body of collaborative studies data when I arrived. What was called Project Three was finishing up at the time I arrived. Project One, as I understand it, was the stimulus for placement of the laboratory at Perry Point. It was to be a Central Office auxiliary, located on the grounds of the VA Center at Perry Point, Maryland, but not administratively associated with the hospital there. It was first formed to organize, monitor, and analyze data from the Lobotomy Project, which later became known Project One of the series of cooperative studies that followed. Lobotomies were common, especially before effective drug treatments became available, but even then the procedure was questioned by many. The VA decided it was time to do something one probably couldn't ethically do today, conduct a controlled study of the utility of the lobotomy procedure for treating psychiatric illness. About halfway through the Lobotomy Project the VA stopped doing lobotomies, and that ended the research

project. As far as I know, the results were never even looked at because the scientific community had decided it was not politically correct, even though about half of the originally planned patient samples had been entered into the study. Chlorpromazine had just come from France in the early 1950's; with it came excitement and controversy about the value of drugs for treatment of patients with major psychiatric disorders. It was decided within the VA hierarchy that nothing should delay undertaking a well-designed controlled study to settle the question of efficacy, once and for all. Project Two of the VA Central NP Research Laboratory was the pioneering multi-center double-blind study of chlorpromazine versus placebo. It became the prototype for clinical trials in psychopharmacology, with double blind, randomized, placebo controlled, repeated measurements. All things that remain state-of-the-art for controlled clinical trials to this day. And it started there at the VA Central NP Research Laboratory where my association with clinical psychopharmacology research also started. When I arrived at Perry Point in 1959, they were just finishing up Project Three, which involved comparative evaluation of the efficacies of five or six new phenothiazine drugs that came along soon after chlorpromazine appeared to be an effective treatment. More important for me was the body of multivariate data these studies produced. It included descriptive rating-scale data from a lengthy instrument authored by Maurice Lorr and others from the VA Outpatient Research Program. It was called the Multi-dimensional Scale for Rating Psychiatric Patients (MSRPP), and I believe it consisted of 63 ordered-category rating-scales, including a few binary items. The VA collaborative studies provided those data on hundreds of patients which I used as a resource for identifying the parsimonious set of basic dimensions of manifest psychopathology underlying the larger body of descriptive data, which in turn served as a basis for development of the BPRS.

TB: So the BPRS was a contribution that actually originated as part of your responsibilities at the VA Central NP Research Laboratory? It has made a lasting impact on clinical psychopharmacology research. Please tell us more for the record how it came about and some of the work you did with it.

JO: The first thing that needs to be emphasized is the important contribution to development of the BPRS that was made by Don Gorham. I was a budding methodologist when I came to Perry Point with no clinical experience. It was Don Gorham who brought the clinical insight and experience. He was twenty years my senior. I contributed the statistical methodology for identifying the primary factor structure underlying

correlations among the larger, somewhat redundant set of rating-scale and binary-response items of Maurice Lorr's Multidimensional Scale for Rating Psychiatric Patients. Don's contribution was clinical interpretation, recommending clinical names for the primary dimensions of manifest psychopathology, and choosing the particular rating-scale nomenclature that constitutes the BPRS today. Actually, there were more steps in development of the present instrument than I have said here, but this should be adequate to provide understanding of the close working relationship that Don Gorham and I had during my time at the Perry Point laboratory. Don left the Lab to become Chief Psychologist at the Bath VA hospital near his retirement home at the top of a hill overlooking Lake Cayuga in upper New York State. The only other thing I would say about what I did with the BPRS is that its popularity in clinical psychiatric and psychopharmacology research today is partly due to my continued use of the multivariate measurement data that it provides to illustrate and evaluate new methods for the analysis and interpretation of clinical data across a decade or more since the BPRS was first published. My uses of the BPRS data included illustrating a new method of direct factor analysis, applications of cluster analysis methods to identify naturally-occurring homogeneous sub-groups of patients with distinct profile patterns, and use of BPRS profile patterns in the search for subtypes that are most responsive to different variants of the newer psychotropic drugs. Time has erased the relevance of much of that work, with orthogonal and oblique rotations of principal axes factor solutions replacing direct factor solutions. The search for specific indications of new drugs within the broader categories of psychiatric illnesses, are largely failing to produce clinically useful results. The work helped, however, to keep the BPRS before the public eye, where new interests in its applicability continued to emerge. My own work having the greatest contribution to wider use of the BPRS would likely be considered introducing it to a larger international psychiatric research audience through collaborative publications with leaders in European psychiatry, which originated, for the most part, from my membership in the CINP. The most important impetus for the BPRS came, however, when Jonathan Cole, as head of the NIMH Psychopharmacology Service Center and subsequent Psychopharmacology Research Branch, foresaw the utility of establishing a central analysis and depository for data collected in NIMH-supported clinical drug trials, particularly those conducted by the group of ECDEU and later NCDEU investigators, where the BPRS was selected to provide a single common thread of descriptive data running across the studies involving antipsychotic drugs and the

Hamilton Depression Rating Scale (HAM-D) for studies in the treatment of depressive disorders. The original Clinical Psychopharmacology Service Center became the Psychopharmacology Research Branch of the NIMH; and the satellite Biometrics Laboratory under the direction of Roland Bonato was established at George Washington University to accomplish the statistical analysis and data management functions originally envisioned by Jonathan Cole and his associates. The leadership of the program at the NIMH Psychopharmacology Research Branch, under one or another of its organizational name changes, was assumed by Jerome Levine when Jon Cole retired and moved to head Harvard's McLean Hospital in Boston. Through all of these evolutionary changes, the BPRS became familiar to an increasingly large proportion of clinical researchers in the United States and for many abroad.

TB: It seems you developed numerous important relationships in those years. Would it be fair to say your relationship with Leo Hollister played an especially important role in directing your career toward clinical psychopharmacology research?

JO: Yes, and membership in the ACNP, as well. Of the early relationships formed at the Central NP Research Lab in Perry Point, Leo Hollister was the most influential in directing my later career toward clinical psychopharmacology research. He was a charter member of ACNP, helped organize the first formal meeting, and later became President of the organization. I was not a charter member, but under his shadow I attended the early meetings and was voted into membership by the 3rd or 4th annual meeting. Leo Hollister was also instrumental in my election to Member and then Fellow of the CINP, which in turn introduced me to leaders in international psychiatry and psychopharmacology research. This led to several collaborations and enduring relationships with leaders in European psychiatry, including most prominently with Professors Pierre Pichot in Paris, Hans Hippius in Munich, and Max Hamilton in Leeds. Charles Pull from Luxembourg spent a year as a young man studying with me while I was professor at the University of Texas Medical Branch in Galveston, as did Filippo Gabrielli from Genoa, Francisco Gomez-Monte from Mexico City, and Peter Reichertz from Bonn who went back to Germany to become a leader in founding of the German Society of Medical Infomatics.

TB: We are still at Perry Point in Maryland. Where is Perry Point?

JO: It was geographically isolated, about 35 miles north of Baltimore and the same distance west of Wilmington, Delaware. Day-to-day interaction was confined to the Point. Some have characterized the social environment as the "Peyton Place on the Susquehanna". But that is all I know

about that. I would like, however, to describe the physical environment I found at Perry Point. It was the most interesting outdoor environment I have encountered throughout my career, rivaling Galveston where I lived following my return to Texas. The Central NP Research Laboratory was located on the Perry Point VA Hospital grounds in an old cement-block building left over from DuPont Company, manufacturing munitions in WW-II. The setting offered numerous enticements. Housing on the hospital grounds, also left from the WW-II war, was conveniently near work and very economical. Our two-story house cost less than $40 per month to rent with heating oil and electricity included. The hospital grounds were on a delta formed by the Susquehanna River where it entered Chesapeake Bay. A boat dock with slips for centerboard sail boats was located about one block from our front door. Sailing was great across delta flats with tall waving sea-grass almost to the surface of the clear filtered water. There were places to sail to, unlike sailing in the Gulf of Mexico after later living on Galveston Island. You could sail around the Turkey Point entrance to the Delaware Cut or picnic on an island belonging to the Army's Aberdeen Proving Ground. Fishing for striped bass and shad was good in the mouth of the Susquehanna River. Herring ran up a small stream on the Point each spring to spawn, and Don Gorham challenged me to wade in the water with chunks of ice floating by to catch the herring in a seine. We netted buckets. After attempting to make pickled herring ourselves, we tried to give the rest to neighbors, but nobody seemed to want them. The one down side was that winters on Chesapeake Bay were cold and damp with lots of snow.

TB: All in all, you seem to have found your position at the VA Central NP Research Lab good professionally and you liked the Perry Point environment. Still, eventually you left Perry Point. Why did you decide to move, and where did you go?

JO: You are right about my professional experience with the VA in Maryland. I had ample resources readily available for my work, had expanding professional interaction both within and beyond the VA, and did enjoy the outdoor environment. I nevertheless had, in the back of my mind, an original graduate-student interest in becoming a university professor. At the same time, I was ambivalent about giving up the relationships and work that I had started at the VA Central NP Laboratory. Two developments seemed to solve my problem. Leo Hollister, with whom I had already begun to form a collaborative relationship that lasted decades, embarked on a pathway separate from that of the ECDEU, in which he had a leadership role form the beginning. I do not know the full story,

but he formed a smaller splinter group of collaborating VA psychiatrists that was more flexible in pursuing the early testing of new drugs and introducing new ideas into the process. He invited me to be involved in the new endeavor from a design and statistical analysis point of view, and I arranged to continue in that role if I moved to Kansas. The other enticement that helped tip the balance was the offer of an unusual opportunity to move directly into a senior faculty position at Kansas State University, even though I had no previous experience as a college teacher. How that occurred is a long story, but it was facilitated by the fact that Professor Harry Helson from my graduate student days at the University of Texas moved to K-State when he retired from UT in Austin. It was he who nominated me to fill a vacant faculty position there. I went to Manhattan, Kansas for a series of interviews after which I was offered a job as Associate Professor of Psychology at Kansas State University, with the side condition that the department chairman at K-State would sponsor and support me in application for an NIMH Research Career Development Award, which I was granted soon after my arrival. Another side agreement was that I could use the award to continue working with Leo Hollister, which I did, while carrying a teaching load of only one course in the fall and one in the spring semester each year. Leo was generous with the credits, and I continued to build a resume of first and second authorships related to clinical psychopharmacology research. In spite of the light teaching load, I discovered I did not like to spend time preparing lectures for relatively few students. Publishing in clinical and methodological journals reaches a lot more people and is, unfortunately, more rewarding for academic advancement and tenure. Life in Kansas was otherwise most enjoyable. The other faculty members and people in the community were quite a change from interactions with the outside community in the Baltimore area. In fact the warm, open, and generous Kansans were like the people in Texas. I learned, upon my return, that Texas was rapidly changing during this period as larger cities and economic interests began to dominate. As an example of the Kansas culture at the time, one of my new faculty colleagues at K-State, Donald Trumbo, and I became acquainted with a family that operated a farm and ranching operation of a couple of thousand acres in western Kansas. Pheasants were especially plentiful out that way, and Don Trumbo and I were invited to come and hunt on their place each year. We went after Thanksgiving dinner and again during the Christmas break and our Kansas host didn't just let us hunt on his property but took the day off to drive us around in his pickup truck, letting us off on one side of a section of sage brush land and driving around to the other

side to pick us up later. There was a lot of sage brush because, at the time, the government was paying to leave it idle for the good of the land and to hold up prices for wheat by limiting production. Sage brush is waist high and is hard to walk through, but a pheasant springing up every 15 feet or so made it quite enjoyable. Pheasants were so plentiful that each trip we got our two-day legal possession limit in morning and afternoon hunts the first day out. I later came to suspect that the land owner operated a hunting guide business on his land during the winter when there was little other work to do, but he treated us like old friends. I also bought an 80-acre farm near Manhattan, Kansas where K-State is located. It had an old two-story house and a storm cellar for tornadoes. I bought a John Deere tractor and planted a garden too large to harvest, but I rented out most of the land to a farmer who planted wheat and soy beans. Regarding the oversize garden, what else do you do with a real farm tractor but to cultivate an oversize garden? I harvested all the produce we could use, gave away to friends and neighbors all they would take, and left the rest for rabbits and coons. I have always needed to counterbalance academic life with something less cerebral.

TB: It seems that you fit into the Kansas State University environment very well, but again you eventually decided to move. What prompted you to move from Kansas?

JO: Out of the blue, I received an invitation to be considered for a job with the University of Texas Medical Branch in Galveston. Truth is that I missed Texas, where I had grown up, gone to school, and where my parents, my wife's parents, and numerous other friends and family remained. I also must admit that I was offered twice the salary I was making at K-State. I accepted the job to become Director of the Research Computation Center of the institution and Associate Professor in the combined Department of Neurology and Psychiatry. There were soon to come, other medical schools in Texas, but the Galveston facility proudly kept its designation as the Medical Branch from a time when the medical school was viewed more like a division or college of a main university rather than a separate institution. It was also the only medical school that continued to receive state funding for hospital operation and patient care. In return, it had an obligation to accept a large quotient of patients from other parts of the state. That was partly a matter of its historical precedent, but also because the school had outgrown its patient base on Galveston Island. The reason why the Medical Branch was located in Galveston in the first place, rather than in Austin with the main university was because Galveston was the only city in the state with a population large enough to support Texas' only medical school

when it was founded in 1889. Life on Galveston Island offered numerous possibilities. After little more than a year our new house on a bulkheaded inlet from the protected back side of the island was completed. The first year we lived there, I caught speckled trout off that bulkhead before I got dressed for work. Our house was about eight miles from the medical center, and many days I would ride my bicycle down the sea wall to work. I had a Sailfish boat on our pier behind the house, and I soon acquired half interest in a 27-foot Norwegian folk boat with a 2000 lb. keel for sailing in the Gulf of Mexico. Later, we built a weekend cottage on the Neches River in the heart of what was to become the Big Thicket National Preserve, and from there I turned to fishing for large-mouth black bass in a couple of the numerous large reservoirs that span east Texas. Life at work turned out to be less tranquil than at the lake or shore. There was a competition between business and academic interests for control of computer resources of the school. The business side had a much bigger computer. IBM involvement in the business operation was great enough to justify six IBM employees on-site full time. The business computer facility was, in the Medical Branch organizational chart, under the Vice President for Financial Affairs while the smaller Research Computation Center was under the Academic Dean. Just days after my arrival, the Board of Regents swooped down on Galveston Island to fire the Dean to whom I was to have been responsible, while the Vice President for Financial Affairs went on to Austin to become Chancellor of the whole University of Texas System. Even within the Research Computation Center a palace revolt was brewing for control. The woman who had previously headed the operation was a close friend of the next appointed Dean, who was also institutional PI on the NIH grant that funded the Center when I arrived. After three years, I decided that administration was not my calling. When I received the first installment of the grant that was to support my work for the next 32 years, I slipped quietly over to my academic appointment as Associate Professor in the Department of Neurology and Psychiatry. At about that time, Neurology and Psychiatry split into two separate departments, and my appointment was thenceforth in the new Department of Psychiatry and Behavioral Science. I was promoted to Professor after four years in Galveston. In the meantime, I was a member of an NIMH Review Committee for which the committee chairman was a Boston University psychiatrist, who had a large NIMH grant to study the stress effects on air traffic controllers of observing “near misses”. I was impressed with his leadership qualities as chairman of the NIMH review committee on which I also served. When the aging

chairman of the UTMB department of psychiatry prepared to resign, I pushed hard, in and around official channels, for the man I had come to know through the NIMH committee to replace him. That was a very big mistake for me and the department as a whole. When my favored candidate was appointed to be the new chairman of the Department at Galveston, he came with the idea he owned everyone in the department. He refused to endorse my grant renewal application, saying he did not want me to do what I was proposing but to be the "department statistician" instead. By coincidence, the retired but politically powerful former President of the Medical Branch was called back into service by the Board of Regents to serve as temporary President in activating the new University of Texas Medical School in Houston. He facilitated my transfer to the new medical school at the same rank, tenure, and title I had in Galveston. I had the site visit on my grant renewal application in Houston before I moved there myself.

TB: You made passing reference to both the ACNP and ECDEU. Could you say something about your involvement?

JO: My recollections are more from participation in the Early Clinical Drug Evaluation Units. I was not a charter member of either organization, but I believe I became affiliated with the ECDEU as a collaborator of Leo Hollister no later than its second or third meeting. At that time, the aim of the ECDEU organization was to provide very early evaluation of new drugs independent of drug company control. The new NIMH Psychopharmacology Service Center, under the leadership of Jonathan O. Cole, was responsible for the origination of the NCDEU program. The initial membership consisted of 10 or 12 senior clinical investigators who were seated around one long conference table on the NIH campus in Bethesda, Maryland. Younger associate members, like I was for the first few years, were seated in chairs around the wall. Actually, "membership" was not as clearly defined as it was for the ACNP, which was organized more like a college fraternity. The senior members of the ECDEU were not only recognized clinical researchers in their own right, but participation was encouraged in fact by support in the form of a grant from the Psychopharmacology Service Center. The discussion at these early ECDEU meetings was largely a kind of "show-and-tell" about what new drugs appeared interesting and what the senior investigators had been doing with them over the past year. In spite of this, a metamorphosis occurred as the research interests of the ECDEU clinical investigators moved from open-label very early testing of new drugs toward more controlled, double-blind studies aimed at demonstrating the efficacy of new drugs in a more controlled experimental design.

The name of the NIMH program and research units supported by it was accordingly changed from "Early Clinical Drug Evaluation Units "to "New Clinical Drug Evaluation Units"(NCDEU). It is important to mention that investigators like those in the ECDEU and ACNP programs were for the most part still acting as individual clinical researchers responsible for all aspects of their studies from conception and design to data collection, management, and analysis. Memberships in both organizations expanded, and cohesiveness began to disappear.

TB: Can you remember who the original ECDEU investigators were when the meetings were held around that single table on the NIMH campus in Bethesda?

JO: I am not sure I can do that with confidence. There was a lot going on in clinical psychopharmacology in the early 1960's. I was privileged to be involved at various levels in three overlapping programs, the ECDEU, ACNP and VA. I interacted with investigators I viewed as key players in all three venues. It has been a pretty long time now, and it is quite possible I will confuse memberships in the ACNP and ECDEU, in particular. I may need your help to fill in where I blank out on this. I remember you were there and I remember the occasions and the contexts better than I am able to separate which particular individuals may have been in one but not the other of the primary groups. In many cases, they were the same individuals.

TB: Am I correct you said that you got involved with ECDEU via Leo Hollister?

JO: Yes, Leo was one of the original ECDEU members. I had established a collaborative relationship with him while I was at the VA Central NP Research Laboratory at Perry Point, and he was chairman of the Oversight Committee for the Laboratory. About the time I was preparing to leave the VA for K-State University, Leo was getting impatient with the cumbersome VA research program and contemplated forming a smaller splinter group of actively collaborating VA investigators. He asked me to join him for the contribution he expected me to make to design, statistical analysis, and methods section of research reports. He received a grant through the ECDEU program to support his proposal for this smaller, more actively collaborating group of VA clinical investigators, and I came aboard to participate. He remained an active member of the ECDEU all the while, and I just accompanied him to those earlier meetings without thinking much about being invited. I was also busy trying to adapt to the new role as college professor, preparing lectures, and beginning to question whether I wanted to be a college professor for the rest of my life.

TB: Can you recall some of the early recipients of the NIMH grants that were a foundation for the ECDEU program?

JO: In addition to Leo Hollister, I think of Heinz Lehmann as probably one of the original ECDEU investigators. Barbara Fish, the lone child psychiatrist in the original group, was the mentor for the younger Magda Campbell in much the same way Leo Hollister was for me. I wouldn't be surprised if Magda had about the same early involvement with ECDEU that I did. Sidney Merlis comes to mind as a probable charter member. An English physician named David Wheatley did outpatient anxiety and depression studies. I remember his faithfully attending the ECDEU and the later NCDEU annual meetings, but I am less confident that he was there from the beginning. Similarly, Karl Rickels at Philadelphia concentrated on a taxonomy of outpatient anxiety and depression in relation to pharmacologic intervention, but he may have entered the ECDEU program about the time I did. I recall his mentioning his NIMH psychopharmacology research grant had the same origination date as mine. Eugene Paykel, an English psychiatrist later at Duke University, had similar interests in defining a taxonomy of anxiety and depression and relating it to differences in drug treatment response, but I think he probably joined the NCDEU program a bit later. Richard Wittenborn was a psychologist identified with the earliest days of the ECDEU program. He later held the office of Secretary-Treasurer of the ACNP for many years. I believe that Dick also authored a rating scale used in one of the earliest VA controlled treatment evaluation studies before Don Gorham and I joined Perry Point, VA which preceded the BPRS. Another psychologist that figured prominently in ACNP history was Albert DiMascio, in whose name an annual memorial lecture is presented at Tufts University. A number of other psychologists with strong methodological orientation supported the ECDEU through administrative roles in the Psychopharmacology Service Center and its successor, the Psychopharmacology Research Branch. A name that comes to mind from that group is Dean Clyde, but there were others as well. I mentioned Ron Bonato in connection with his work as head of the NIMH/George Washington University satellite computer center, founded to accumulate assessment data for patients in the NCDEU clinical trials. I don't know when Jerome Levine joined the intramural group because in a bureaucratic environment it takes even talented young people time to reach a level of visibility, but there is no doubt about the contribution he ended up making as successor to Jonathon Cole. Alice Leeds entered the picture at about that time, was a friend and critic of everyone, and will be remembered for her editorial role in helping the NIMH

supported Psychopharmacology Bulletin reach the audience for which it was intended. I liked to publish my work in that journal because I was communicating to the clinical investigators with whom I had an identity. I have strayed from the question of who were the founding participants in the ECDEU program. Can you recall me of others that have failed to recall?

TB: George Simpson and Don Gallant were there from the beginning.

JO: They were definitely there early on. I believe there were no more than about eight or ten original recipients of the Early Clinical Drug Evaluation Unit grants. I have undoubtedly named a number that were not in that group at the beginning, but I remember them all as contributing in recognizable ways to shaping the course of early clinical psychopharmacology research through participation in the ECDEU, ACNP, or in both. There was, however, another psychiatrist I believe Jonathan Cole may have brought aboard the Psychopharmacology Service Center staff to interact specifically with the ECDEU investigators. He was not slow in gaining visibility; but, as I recall, he wasn't very popular in that role. I can't recall his name and I am not sure he was a member of the NIMH in-house staff.

TB: Could you be thinking about George Crane?

JO: I am sure that is his name. He was an astute clinician onto something important about serious neurological side effects of the early phenothiazines that ECDEU investigators were not eager to hear about. I don't know whether George Crane is responsible for the naming, but he was certainly important in linking the frequent occurrence of tardive dyskinesia to psychiatric drug treatment. When he presented his observations at an ECDEU meeting, he was almost ridiculed out loud in the meeting and certainly in an after-hours meeting of several members at a cocktail lounge of the Bethesda Naval Hospital across the street from where the NIMH was located. I was quite young, and naturally my opinion mirrored that of the senior members I was pleased to accompany. George Crane's popularity was not increased when he presented the plan for ECDEU participants to collect specific data that could be combined across centers for further analysis at the George Washington University Biometrics Laboratory. The BPRS was to be used in studies involving the testing of antipsychotic drugs and the Hamilton Depression Scale was to be the common data collected across studies involving depressed patients. I guess that none of the independent-minded senior investigators liked to be told what they were to do, and maybe it was contributed to by how George Crane came across. He just didn't have a politically-correct way of doing things. That is too bad because

his contributions to the ECDEU program and to clinical psychiatry were really important.

TB: We have talked about your early involvement in ECDEU and NCDEU. You did mention the importance of relationships that you developed with European psychopharmacologists and psychiatrists through your affiliation with the CINP. Would you enlarge on that?

JO: The CINP has not been just another organization for me. It has produced collaborations that introduced much of the world to the Brief Psychiatric Rating Scale through a series of papers in which it was used to compare and evaluate the consistencies and differences in psychiatric diagnostic concepts in different countries. Of even greater importance to me personally has been the associations formed with prominent psychiatrists, psychologists, and psychopharmacologists in different countries. While my difficulty in distinguishing between the important early associations in ECDEU and ACNP has been apparent, that is much less true of the early influences on my personal and professional career that can be attributed to affiliation with the CINP. I mentioned some of their names earlier, but it might perhaps be interesting to mention a few personal memories of those important influences on my life and thinking. Somehow, I see them more clearly as individuals than many who were closer to home. A rather humorous incident occurred at a WHO sponsored meeting in Belgrade early in my affiliation with CINP. It was at a meeting of several days duration, and Max Hamilton was the appointed chairman. His autocratic handling of discussion and the discussants began to create a feeling of resentment as the meeting went on. As the acknowledged pioneer in clinical rating scale development and due to the popularity of his HAM-D rating scale for depression, he may have felt competitive regarding the BPRS. From the chair, he verbalized his opinion that the different rating constructs in the BPRS were not adequately defined. He punctuated his criticism by singling out the BPRS rating construct Hostility and saying in a raised voice “Hostility, I don’t even know what that means.” The crowd in attendance broke into a tension-relieving round of laughter. I would not even mention this except for the lasting friendship Max Hamilton and I developed after that. He visited me in Galveston twice and stayed as a guest in our home. He was really warm and personable when you got to know him. Another lasting memory from that WHO meeting in Belgrade, which was attended by many CINP members, was a planned dinner in an old fortress on a high bank overlooking the Danube at the village of Novi Sad. I was seated beside Dr. Oldrich Vinar on the bus that took us there, and I remember well it was the day we all heard of the Russian

takeover in Prague. No one knew that it was to be the last occasion any of us would see Dr. Vinar for a long time. He went back to Prague and was not permitted to leave the country for years. A psychologist named Engelsman had accompanied Vinar to the Belgrade meeting, but he didn't return to Prague and went to Canada instead. I think he may still be there.

TB: Yes, he has remained in Canada and is working there.

JO: Reflecting on what I have been saying about my European acquaintances, it is interesting how differently I have spontaneously designated them a formal title or not. Most are professors in their home institutions. I have used no rank or title in mentioning our ECDEU and ACNP colleagues. Most are friends whom I have known for years. It is customary for me not to identify friends by title. I might use titles in introducing them, but not when I identify them in conversation. On the other hand, there are certain European colleagues who are always Professors in my mind, even though I have known them long and consider them friends as well. In particular, there are Prof. Pichot and Prof. Hippius. Nevertheless, I have always been awkward in making introductions. I have never forgotten when I introduced Professors Pichot and Hippius to my wife the first time she accompanied me to a meeting where both were present. I believe it was probably CINP. In attempting an introduction I said, "Peggy, this is Professor Pichot and this is Dr. Hippius". Try to work your way out of that one! We were, in later years, invited to the homes of each of them, so I suppose I have been excused. But I haven't forgotten that faux pas to this day. There are people in Europe that remain always Professors. I actually met Prof. Hippius somewhat earlier when he was at the Free University in Berlin. He had invited me to consult and perhaps to give a talk, I don't remember. Soon after that, he was appointed to Kraeplin's former chair in Munich, where he invited me to give a talk and entertained my wife and me for dinner in his home. I remember that visit because it was the beginning of Christmas season when the local vendors were constructing their stalls for the Christmas Market in the center square in Munich. It began to snow, making a picture of the Christmas Market in my mind like I have seen on postal cards from friends visiting there in later years. European collaborators and acquaintances, one way or the other tied to CINP, have been so generous and personally cordial to me that I have debts I can never repay. Some were senior academicians like Giovanni Cassano in Pisa, who I identify in my mind as among early proponents of computer technology in European psychopharmacology and whose conversion of an authentic farm house, with quarters for cows included, was an elegant setting

for entertaining groups of visitors, in which I was included on occasion. From an historical perspective, I remember Jules Angst in Zurich giving me a personal tour of the hospital he inherited when named to the Chair Bleuler previously occupied. Others, like Professors Gioberti and Rossi in Genoa, Pichot in Paris, and Jose Carranza in Mexico City helped to arrange for their junior associates to study with me in the US, mostly at the UT Medical Branch in Galveston. Among them all, Prof. Pierre Pichot stands out for his long and generous support of my career and what I value as a personal relationship. I am sure that is not unique for him, but I value it nonetheless. He has personal relationships with psychiatrists and psychopharmacologists throughout much of the world without letting international politics stand in the way. There are many memories that remain from long acquaintance with Prof. Pichot. A scholarly French professor, with pipe and hat, he was active in his local medical society and international psychiatric circles as well, but on Friday afternoons he closed his office to catch a train for the weekend in a small village south of Paris where he had a cottage and a different set of acquaintances. My first memory of him is associated with attempts to meet for an appointment at his office in the hospital of Saint Anne. I knew it was in the region of the Sorbonne, but I had failed to get adequate instructions on how to find him. I wandered into a likely looking building with a long dimly lit corridor ending with light coming from a room on the left. When I entered, I saw two scholarly gentlemen bending over manuscripts or maps on a table in an otherwise bare room. After I waited quietly before clearing my throat to interrupt them, they inquired of my mission. I asked if they could direct me to the office of Professor Pichot. They could not seem to understand who it was I said I was looking for. After several attempts to repeat, one of them produced a tablet and pencil and asked me to write down the name. They looked at what I had written and exclaimed in unison “Ah, Pichot!”. It sounded like what I had been saying, but obviously not to the French ear. Another memorable visit to Prof. Pichot’s office occurred on the very day of the beginning of the student riots in Paris around 1970. I had taken a room the night before at a two-star hotel on Rue Ecole about two blocks west of the Sorbonne. When I stepped out the door in the morning, I saw a double cordon of police in riot gear, holding small grey shields, was blocking the avenue in front of the university. I don’t remember how I got in touch with him, but Prof. Pichot said to wait at the hotel and he would send a resident to take me by car around the disturbance to his office. The morning was quiet enough at his office in the Hospital, and he suggested we go to a nearby café for lunch if it isn’t too crowded. When we

walked in, there were only two other occupants at one of the tables in an otherwise empty café. When we left to go to his apartment, which was up the hill from the Sorbonne and across street from the French pantheon, a policeman stopped us at the corner. We could see the crowds below us down avenue St. Michelle and smell tear gas in the air. After some discussion in French, the officer approved of our intent to continue in a direction away from the crowd and toward Prof. Pichot's apartment further up the grade, where we visited for a l while. He took me across the street to visit the stark interior of the pantheon shrine, and then directed me how to get back to my hotel. I followed his instructions and arrived without incident. But that wasn't the end of the day for me, although I never admitted the rest to Prof. Pichot. I donned a windbreaker I imagined would make me look like a foreign correspondent, if only I had an arm band like they wore. I joined the excitement, marched down St. Germaine behind a student leader who was being escorted for negotiations with authorities, and got caught in a trap laid by police. I bravely lay down on the pavement with arms shielding my head as the police with rubber batons continued whacking students, right and left. I ended up at a glass enclosed café about a block above where students were burning a news stand on St. Germaine, and stacking small foreign cars to block the entry of emergency vehicles. Police were responding with tear gas by then. From my vantage point inside the café, with another glass of wine, I watched something that changed the character of the Left Bank forever. It was students, with handkerchiefs shielding their faces from the tear gas, using iron bars to break up the bricks that surfaced the Left Bank street for use as stones to throw at the police. The streets have since been repaved with asphalt and riot police have retreated to large blue busses with windows shielded by iron grating, where they remain today. There is a quite different occasion I like to think of in my appreciation of Prof. Pichot. He visited me in Galveston, and I recall his amusement at the Christmas decorations adorning palm trees on the boulevard into town. It turned out he had also been invited to visit NASA by the chief medical director, Charles Barry. I drove Prof. Pichot from Galveston, and to my pleasure, was invited to join him on a guided tour around the NASA facility. We were met at the entrance by a large black limousine with red VIP flags on the front fenders and our auto tour ended at the NASA space museum. After examining successive early space vehicles that were on display and sitting in the driver's seat of the lunar-lander simulator to view the approaching moon surface, we started a tour of exhibits representing steps of the space program from earliest days. As a bonus for

me, the first section of the exhibit focused on Sam the "space monkey" and featured several pictures of the late W. Lynn Brown, who was my graduate professor and the one who brought me with him to work at the Radiobiological Laboratory at Balcones Research Center near Austin. It was an emotional surprise to come such full circle from where I started as a graduate student at the Radiobiological Laboratory in Austin, Texas to that visit with Prof. Pichot to NASA. Not many miles apart, but a lot of time.

TB: Could you tell us about your present interests and how they developed?

JO: I mentioned my doctoral degree was in General Experimental Psychology. That gives a person a rather broad background in different areas of scientific endeavor. From there I followed where opportunities led for several years. Apart from my early participation in psychopharmacology clinical trials, where I was directed to provide support for statistical analysis and participate in writing methods and results sections for manuscripts I have been guided by the notion, "If it isn't novel or controversial, it probably is not worth doing." That has pushed me in the direction of controversy with authority or established practices on numerous issues. These included the use of least squares regression to produce tests of significance in unbalanced factorial designs that are comparable to tests produced by the same cross-classification design with equal cell frequencies. Also, correcting for chance baseline differences in randomized or naturalistic treatment conditions, or conditions favoring the analysis of simple endpoint difference scores versus complete regression analyses for comparing treatment responses in repeated measurement designs. My present work is no less controversial, but to explain it really requires consideration of where it all started and of computer simulation methodology that has provided the criterion for evaluating comparative validities of different analytic procedures. My concern is with the development and evaluation of simpler methods for analysis from controlled repeated measurement designs that clinical investigators who do comparative treatment research can themselves understand. It has roots that extend back to my early work as a graduate student at the UT/USAF Radiobiological Laboratory where I developed hands-on familiarity with classical repeated measurements analysis of variance. My work at the VA Central Neuropsychiatric Research Laboratory at Perry Point introduced me to problems for use of classical analysis of variance to analyze data from controlled longitudinal studies involving dropouts. My move to K-State University introduced me to FORTRAN computer programming, because there was no one else to do it for me in the open-shop computer environment there. That was

the best educational experience I ever endured, and it was while I was supposed to be the teacher. If I do say so, I became expert in computer programming which, when I moved to the University of Texas, started me on the path to developing a series of increasingly powerful and flexible procedures for simulation of various conditions found in controlled longitudinal treatment studies. My introduction to correlation structures while studying multivariate methodology at the Psychometric Laboratory of the University of North Carolina facilitated consideration of different patterns of correlated error when simulating realistic controlled clinical trials. Finally, my career-long close association with clinical researchers at different levels of experience and accomplishment has given me unusual appreciation for the lack of preparation and motivation clinical investigators have when it comes to understanding the complex statistical modeling procedures increasingly promoted for analysis of data in studies they design and conduct. My present concern is not with individuals who collect data on 6 or 8 patients who are to be pooled into a large drug company sponsored study but it is with the remaining clinical investigators who desire to pursue unique interests using sample sizes that are feasible to acquire in a reasonable time in local clinical settings. It assumes such investigators desire to understand a procedure that determines what they can legitimately conclude about results from their studies. My perspective is rooted in classical experimental design and analysis of variance I practiced laboriously at the Radiobiological Laboratory while a graduate student at UT in Austin in the mid 1950's. It was taught from a classic text authored by educator/psychologist Lindquist at the State University of Iowa. The text contained a major section on "mixed models" that developed the correct error terms and tests of significance for fixed and random effects in a variety of increasingly complex repeated measurements designs using rather straightforward algebraic and arithmetic proofs. Simultaneously, a mathematical statistician name Eisenhart at the National Bureau of Standards in Washington, DC developed identical solutions using a more complex "components of variance" approach. The fact that later popular texts on experimental design and analysis of variance for psychologists and behavioral scientists, such as the widely used text by B.J. Winer, incorporated the components of variance approach indicates a deference members of applied disciplines tend to have for mathematical statisticians. As an empirical psychologist relying on realistic simulation methods, I clearly do not share that problem.

TB: Are you suggesting you do not believe complex statistical modeling approaches are better than simpler approaches which are better

understood by clinical investigators who actually conduct most controlled treatment evaluation?

JO: I did not start out questioning the superiority of the mathematically complex statistical models and the equally complex maximum likelihood calculations. I am referring to tests of significance for differences in treatment effects in randomized repeated measurements designs that are based on Generalized Linear Mixed Models (GLMM), such as those produced by the SAS PROC:MIXED computer program, which has become so popular with statisticians working in the drug industry. No, my problem is that the GLMM procedure is not understood by clinical investigators who are responsible for executing, analyzing, and reporting results from comparative treatment evaluation studies in clinical psychopharmacology.

TB: If the mathematically complex statistical modeling procedures are not widely understood by the investigators in clinical psychopharmacology, are there procedures that you would recommend as an alternative?

JO: The approach I and a succession of collaborators has taken can be broadly classified as analysis of "summary statistics" which combine observed repeated measurements into single composite scores that meaningfully represent treatment effects to be tested for statistical significance. It would be wrong not to recognize the frequent use of summary statistics by biopharmaceutical statisticians, as dependent variables for testing the significance of treatment effects in repeated measurement drug trials. Academic statisticians such as Helena Kramer at Stanford Medical School have published papers recommending such procedures for the analysis of "messy data" in less well controlled longitudinal studies. Analysis of covariance (ANCOVA) has been proposed by some as a way of correcting for missing data due to dropouts. The most commonly used summary statistic has been an ordinary slope coefficient fitted to the available measurements for each study subject. Simple and familiar tests of significance for difference between means of the slope coefficient are then employed to test the mean rates of change for subjects in two or more randomized treatment groups. A problem with most of the work that has been published on these procedures, and especially expositions related to the more complex generalized linear mixed model analyses, is they have provided worked examples or results from calculations applied to a single data set. Our contribution has been the use of simulation methods to evaluate how good the solutions really are.

TB: You have mentioned "simulation methods" several times in this interview. What are they in the context you use them?

JO: Simulation of clinical trials begins with generating raw data that looks like you would expect from an actual clinical study. The data generation involves use of an equation with coefficients, called parameters, which are controlled by the user to inserts into the generated data you would expect to be made by fixed factors, e.g., treatment differences and effects of time in treatment, as well as random effects including sampling variability, carry-over effects and random occurrences of missing data. When you print out the simulated data file, it should look like you would expect real data to look under the circumstances considered. If not, you have an opportunity to change parameters in the data generation equation and generate a new batch of simulated data that looks more like you would expect. The advent of high-speed computers has made possible the use of simulation methods to evaluate and compare the validities of alternative statistical procedures. The procedures we have been interested in test the significance of difference between effects of treatments, in a repeated measurements design, and in the presence of dropouts and autoregressive correlation structures for the simulated data. We refer to the simpler procedures as two-stage analyses. In stage 1, a linear slope coefficient is fitted to the measurements for each subject and weighted by the time the subject remained in the study before dropping out or completing the trial. Stage 2 involves application of common analysis of covariance, ANCOVA, to test the significance of the difference between group means with baseline scores and time-in-study entered as two linear covariates. High speed computation permits the whole procedure from independent data generation to tests of significance on the summary statistics to be repeated many times in relatively little time. The power of the test of significance is then estimated from the relative frequency of rejection of the null hypothesis across the series of hundreds or thousands of simulated data sets. Where the Type 1 error rate is to be calculated, no true treatment difference is introduced into the generated data that are analyzed. The accuracy of estimates of Type 1 error or power increases with the number of sample data sets generated and analyzed and can be as small as one considers important for comparing different analytic procedures.

TB: How satisfactory did you find this “simple two-stage analysis”?

JO: The first formulations of the simple two-stage analysis we evaluated did not weight the individual slope coefficients by time-in-study for dropouts, and the power of tests for differences in the mean slope coefficients was observed to drop off substantially as the frequency of dropouts increased in different simulated conditions. This was rectified by including weighting for time-in-study in the recommended analysis.

Similarly, the value of more numerous repeated measurements was shown to decrease with increase in departure from a uniform correlation structure for the simulated data. In fact, the comparative results indicated that tests on simple difference between baseline and last measurement for each subject provided greater power than tests on slope coefficients fitted to all of the available measurements when the correlation structure of the repeated measurements was strongly autoregressive. By "strongly autoregressive" I mean the correlations between measurements close together in time are much larger than the correlations between measurements further apart. Given that one considers the correlation structure of the repeated measurements in choosing between a two-stage analysis of weighted slope coefficients fitted to all of the available measurements and a two-stage analysis in which simple difference scores replace the slope coefficients as the dependent variable for a familiar ANCOVA test of significance, we feel quite encouraged by the results for both Type 1 error protection and power.

TB: If I understood you correctly you prefer to use simple over complex statistical methods. Have you employed the simulation methodology to compare validity of the simpler and more complex procedures?

JO: We have done a number of comparisons under different simulated design, data structure, and dropout conditions. That is where we unexpectedly got ourselves in another controversial situation. We did not expect the simpler two-stage procedures to be superior to the "state-of-the-art" procedure for analysis of data from clinical trials with missing data due to dropouts. All that concerned us was that the simpler methods should not have seriously inferior validity. Monte Carlo runs of 1500 or 3000 simulated sample data sets with different correlation structures, linear or non-linear patterns of true mean change, and different random or non-random dropout conditions were generated, and each of the data sets was analyzed by both the simpler two-stage and more complex GLMM procedure. The simple two-stage analyses of both weighted slope coefficient and simple endpoint difference scores evidenced appropriate Type 1 error protection under all of the conditions examined, whereas complex "state-of-the-art" GLMM random effects model formulation using error structure specification, recommended by the author of the SAS PROC.MIXED procedure, revealed non-conservative error protection about half the time. More to our surprise, in no case where the more complex GLMM analysis provided appropriate Type 1 error protection was its power superior to that of a simple two-stage analysis, the choice of which was based on the error

structure of the simulated data. Much of this work has been published or will, we hope, be published in good time.

TB: This is a good time to conclude the interview with Dr. Overall on an optimistic note.

JO: I'm afraid I have gone on much too long as result of my identification with clinical investigators whom I believe are essential to the continued improvement in treatment of psychiatric disorders. The work we are doing now has proved quite controversial, and I appreciate the opportunity to call it to the attention of anyone who might be interested. The simple two-stage analysis still lacks an objective rule for choosing the number of measurements to include in the research design or in the Stage 1 definition of change, even when more have been obtained. We continue to work on that, so please stay tuned.

TB: I would like to thank you very much John for sharing all the information about your life, education, and career.

JO: I hope we'll see one another again before too long, Tom.

EUGENE S. PAYKEL

Interviewed by Thomas A. Ban
Acapulco, Mexico, December 11, 1999

TB: This will be an interview of Professor Eugene Paykel* for the archives of the American College of Neuropsychopharmacology. We are at the Princess Hotel in Acapulco, Mexico. It is December 11, 1999. I am Thomas Ban. Let's start from the very beginning: where and when were you born and brought up?

EP: By origin, I am a New Zealander although it has been many years since I have lived in that beautiful country. I mainly am English, but have affiliations to many parts of the world. I was born in Auckland, New Zealand and my father was a businessman who had been a student at Harvard and met a young concert pianist from New York, whom he later married and who is my mother. I was educated in Auckland, New Zealand and I went to medical school in what was then the only medical school in New Zealand, Otago University in Dunedin. I was born in 1934, and I was a medical student from 1951 to 1956. After two years as a house physician in Auckland, I had the wanderlust, like many New Zealanders, and I got on a cargo ship to England for further training. I am one of the past generation able to make that journey, half-way across the world, as a ship's doctor for free passage. So I was ship's doctor with a crew of seventy and twelve passengers crossing the Pacific Ocean, through the Caribbean and up to New York where we spent a week at Port Newark before crossing the Atlantic in winter to London. I spent a few years training in internal medicine in England which was a common pattern in those days for young ambitious British psychiatrists who wanted to work in the best teaching centers.

TB: When did you start training in psychiatry?

EP: In 1962, I started as a resident at the Maudsley Hospital, London. I was there for three years as a resident and for one further year. That was a very stimulating environment, particularly in those days. The Professor was the late Sir Aubrey Lewis who was a rather austere and forbidding man on the outside but quite warm on the inside. The number of bright stimulating young people were working there was phenomenal. I was blessed with highly stimulating contemporaries and an environment that encouraged critical thought and academic development. Still infected with wanderlust, in 1966 I crossed the Atlantic to Yale University in New Haven to undertake research. That turned out to be a very fruitful time.

---

* Eugene S. Paykel was born in Auckland, New Zealand in 1934.

I stayed almost five years, got married to my English girlfriend and our first child was born a few months before we returned home to England in 1971.

TB: With whom did you work at Yale?

EP: With Gerry Klerman, and I was very fortunate I chose him and that he chose me. We set up what became the Depression Research Unit at Yale. It started with a small grant from NIMH and gradually increased. I was responsible for hiring, with his approval, Myrna Weissman, starting what became one of the most glowing marital partnerships in American academic psychiatry.

TB: Could you say something about the research you did at Yale?

EP: We undertook a variety of studies in depression and this was the start of my own research career. We were interested in classification of depression which, at that time, was a widely published topic and still the subject of controversy, centering, on the distinction between endogenous and reactive depression but also involving other aspects. An off-shoot of that was a cluster analysis, one of the early applications of that technique in psychiatry. On a sample of one hundred and eighty five depressives, who had been studied in great detail, we were fortunate to gain access to a new cluster-analytic classificatory program which ran on one of the most powerful computers in existence, an IBM 360. The program took some hours to run at night but it would run today on a desktop computer without any problem. The object was to explore the classification of depression using a technique that was more appropriate than the factor analytic techniques which had been used so far. Factor analysis produces dimensions of variation, but we wanted to find groups of subjects. It turned out well and we identified one psychotic group and three non-psychotic groups which could be called neurotic. One group was characterized by anxiety with depression and a chronic history, another by hostility and a third group of young people with fluctuating depression and a background of disturbed interpersonal relationships. Perhaps the most enduring aspect has been the demonstration that what had been regarded as a single group, neurotic depression, was rather diverse. Since that time, usage of the term neurotic to describe depressives has dropped out of the literature. A second study of the relationship of life events to depression.

TB: Could you tell us about the kind of information your analyses were based on?

EP: This was a comprehensive set of information on a diverse group that included detailed clinical characterization of patients based on about thirty-five symptoms derived by the Clinical Interview of Depression,

elaborated from the Hamilton Depression Scale. In addition there was information on history of onset, previous history, neuroticism on a scale called the Maudsley Personality Inventory, devised by Eysenck, which has stood the test of time; and a Life Events Interview, which we designed ourselves as a semi-structured schedule to characterize events at the onset of depression with precision. That led to the more expanded life event work. It seems difficult to appreciate now, but at that stage, the issue of whether life events played any role in the onset of depression was hotly disputed. There were two schools of thought; one regarded all depression as constitutional and biological and would admit no room for life stress; the other school emphasized psychological factors, whether recent or in early upbringing but was not prepared to admit a place for constitutional or genetic factors. The only way to cut through this problem was to undertake proper empirical studies. We were fortunate that a large epidemiological study with more than nine hundred subjects from the general population was being carried out by the sociology department. I was able to incorporate in that study the same life events interview we used for the six months prior to the clinically defined onset of depression in our study. Analysis of the study showed clear differences in event occurrence between our depressed patients in the six months prior to onset and the general population controls, matched on social characteristics. Prior to onset of depression there were more events and particularly certain kinds of events, characterized as undesirable or "threatening". Also, prior to depression there was an excess of events that involved an exit from the social field, a sociological concept involving a departure of somebody, creating one kind of loss. That was the first published study looking at comprehensive life events by a careful interview schedule prior to the onset of depression compared to matched controls. It was my first citation classic!

TB: What year?

EP: 1969. The title was, *Life Events and Depression,* published, in the Archives of General Psychiatry. It received a lot of attention at the time. That was preliminary to a second study aimed at a psychopharmacological question. By the later sixties, the antidepressants had been available since the late 1950s and there was good controlled trial evidence for considerable benefit in the acute treatment of depression. The common pattern of using drugs was to treat for three months since that is the way we treat many acute disorders, but not to continue the antidepressant. But, clinically, it was becoming apparent there were high relapse rates. It was not yet conclusively shown whether that was due

to pharmacological withdrawal from the drug or whether psychological factors could have been important since cessation often heralded discharge from care of a psychiatrist. So we designed a controlled trial that would treat patients acutely with amitriptyline for two months. Those who responded were assigned randomly either to continue the antidepressant for six months, or to withdraw double blind onto placebo. A third group withdrew onto no medication, since that is the natural situation in a clinic. We also decided to enrich the study by incorporating a group on psychotherapy. We settled on case-work orientated individual therapy by social workers. It was a form of therapy that later became Interpersonal Therapy, although that was not a term we used then.

TB: Who else besides you and Gerry was on the research team?

EP: By that time, Myrna Weissman and Brigitte Prusoff, a statistician, had joined the group. So, the study was turned into a six cell factorial design, drug versus placebo versus open withdrawal, with or without the psychotherapeutic modality that later became Interpersonal Therapy. Like all such studies, it took several years. Long-term trials are also long term tasks for the investigators!

TB: What did you find?

EP: The findings were clear-cut. Continuing antidepressant treatment was beneficial in preventing relapse. Relapse wasn't entirely abolished, but it was better than halved by continuing antidepressants for six months. There was no difference between withdrawing to placebo and withdrawing to no medication, so placebo effects were not important and this was undoubtedly a drug effect. The psychotherapy had no effect on relapse but it did have an effect on improving social function and interpersonal relationships by the end of the study. There was a synergistic effect in that medication prevented relapse and the psychological treatment improved relationships and function. The best outcome was to receive both. That has been my belief ever since, which will not surprise you. So that was the culmination of the Yale studies. We had by that time, launched a large series of studies on life events and other psychiatric disorders. We looked at the treatment of suicide attempters and we studied other themes as well, but I returned to England, with my wife and our four months old child, to an appointment at St George's Hospital Medical School in London.

TB: So from Yale you returned to London and worked at St George's Hospital Medical School.

EP: That medical school has a very interesting history. It developed, as most of the London medical schools did, in the late eighteenth century; Jenner, the pioneer of vaccination had been a student. Hanging in the

library is the skin from Blossom, the cow from which Sarah Nelmes, the milk maid, contracted cow-pox having been protected against smallpox. After two or three years, in which I was still heavily involved with the Yale studies, I embarked on my own research program. Still interested in depression type and treatment outcome, I started work on MAO inhibitors. There had long been an interest in whether the MAO inhibitors benefited a particular group of depressives.

TB: Were they considered to be particularly effective in atypical depression?

EP: That view came from William Sargent, a charismatic clinician, not a researcher, at St. Thomas' Hospital in London, and people who worked with him. They coined the term "atypical depression" to describe a type of depression they felt, on clinical grounds, showed the best response to MAO inhibitors. It was characterized by anxiety, increased appetite, increased weight and increased sleep, as opposed to the typical insomnia and loss of appetite that occurs with other types of depression. What underlay this was the idea it wasn't endogenous depression and was, therefore, not typical. I was fortunate to obtain an American grant from NIMH to undertake a controlled double-blind trial of phenelzine versus amitriptyline versus placebo, in a sample of outpatient depressives and mixed anxiety depressives at St George's.

TB: What did you find?

EP: The findings of that study were that phenelzine was surprisingly effective and comparable in efficacy to amitriptyline. When we looked at subjects benefiting particularly from one drug or the other by comparing drug versus placebo differences it was subjects with anxiety in addition to depression, who showed selective benefit from phenelzine. That was one of the findings supported by a number of other studies in the literature, including studies of panic disorder.

TB: What assessment instruments did you use?

EP: A wide variety of clinical ratings. We used the Hamilton Scale, our own Clinical Interview, the Hopkins Symptom Checklist self-report version, and the global clinical impression of severity and improvement. Also we collected quite a lot of history data, and made an attempt to classify or sub-classify depression on the basis of some short definitions within that outpatient spectrum.

TB: In what doses did you use the drugs?

EP: They were what I would describe as standard British doses, amitriptyline one hundred and fifty milligrams daily and phenelzine sixty milligrams daily. The more predominant view in the eighties and the nineties has been that increase in appetite and increased sleep characterize MAO inhibitor responders. To some extent that is true, but evidence

regarding anxiety in Sheehan's excellent study, suggests some anxious patients benefit preferentially from MAO inhibitors over tricyclics. In those days we did not have available the serotonin reuptake inhibitors which also seem to benefit patients with anxiety more. Subsequently I became interested in milder depression in general practice. By this time we were getting into the early eighties. An active question, both in Britain and worldwide, was whether the antidepressants benefited the milder depressions treated in primary care. In Britain, in those days and since, only about one in ten patients with depression are referred to a psychiatrist and nine out of ten are treated by general practitioners. In most countries, including the USA, the majority of the treatment of depression is not from psychiatrists, but internists and other kinds of physicians. Often, depression in general practice is milder and we had no evidence, in spite of widespread use of the tricyclics, they were beneficial in those milder depressions. Particularly, we had no evidence as to any characteristics that might distinguish patient gaining benefit from the antidepressant from those who were not. So we undertook a controlled trial of amitriptyline versus placebo in general practice in a wide area of south London. I was fortunate to have as collaborator Professor Paul Freeling, a very eminent figure in academic general practice in Britain. We enrolled more than twenty general practitioners, who agreed they would identify patients with depression that we could interview and randomly assign double blind to amitriptyline or placebo. The target dose of amitriptyline was one hundred and fifty milligrams daily and the median dose was one hundred and twenty five milligrams daily, a little lower. Subjects received six weeks double blind treatment and then assessed by a psychiatrist again, with the same standard rating scales. There were clear cut results, which surprised us.

TB: What did you find?

EP: Amitriptyline was considerably superior to placebo in mild depressions. The mean Hamilton seventeen item total score at inclusion was a little below fifteen, so the majority of patients would not have satisfied the inclusion criteria in standard studies assessing new antidepressants in psychiatric outpatients. We looked at the group showing benefit of drug over placebo and those for whom drug was no better than placebo. Over a wide variety of characterizations, there was no selectivity, except in one respect, and that was initial severity. Patients with major depression, probable or definite, on the Research Diagnostic Criteria showed clear superiority of drug over placebo. Patients with minor depression did not. When we characterized subjects further on the initial Hamilton scores we found in patients who scored below thirteen,

the drug was not superior to placebo but in those patients with scores of thirteen and over it was. The maximum scores were in the mid twenties. There seemed to be this clear severity threshold, which extended a little below major depression but did include the more severe end of minor depression. That took me to the mid eighties.

TB: When did you move to Cambridge?

EP: In 1985, having been a full professor at St. George's, I moved to Cambridge to succeed Professor Sir Martin Roth as head of the department, the equivalent of chairman of psychiatry in Cambridge. My first few years were heavily engaged in administration and building a department rather than research. I had been undertaking at St. George's, in collaboration with the department of pharmacology, a series of platelet receptor binding and neuroendocrine studies, looking at receptor sensitivity in depression. We carried those on in the first few years at Cambridge, but not beyond, because the results had been largely negative. I was becoming disaffected with the platelet as a mirror of the brain. Although in the late seventies and earlier eighties it had been attractive since it shares some of the receptors and the uptake mechanism for serotonin with the brain.

TB: Didn't you also get involved in epidemiological research in the elderly?

EP: I undertook some dementia epidemiology. There were strong epidemiological collaborators in Cambridge and we carried out large scale studies of elderly subjects in the general population. One study was of two thousand subjects aged over seventy five at the time of inclusion. That is a cohort which was started from 1985 to 1987 by a young Australian, who was working in Cambridge, Daniel O'Connor, which we kept going. The survivors are still being studied thirteen to fourteen years after the original study. They are a smaller group now because they were all over 75 at the time of the first study. We found rates of dementia, probably Alzheimer's, though you can't be sure in community studies, with incidence rates which doubled approximately every five years in age, reaching high rates in subjects over 90. There was not a hard and fast borderline between mild cognitive impairment and more severe dementia in the older groups; it was more like a continuous distribution. It looked as though the clear cut separation we find in younger people, between those who have Alzheimer's and those who don't, began to get fuzzy in old age, suggesting a more continuous process. That has linked with brain banking work. We were fortunate that the brain bank started by Iversen and Bird in Cambridge was transferred with MRC funding to the department of psychiatry. With that, and with the help of a very creative research nurse, we were able to work

with families and get their agreement to post mortem studies so some of that is still going on. It has extended to molecular biology as well as neuropathology.

Meanwhile, I returned to my primary interest, which was depression, and in the late eighties we decided the important theme was longer term outcome and what to do about it. It had become apparent from the NIMH collaborative study by Keller et al., the studies by Lee and Murray at the Maudsley Hospital and the study by Kiloh in Sydney, that the longer term outcome, which we had assumed would be good, was not. There was good controlled evidence that long term treatment on a continuation or maintenance basis, either with an antidepressant or lithium, cuts down markedly rates of relapse and recurrence in affective disorder. On the other hand, naturalistic follow up studies found high rates of relapse and recurrence in spite of the availability of these treatments. So the broad question, at the beginning, was what was the explanation? There were several possibilities. First was the time delay that inevitably elapses when undertaking long term follow up studies. It was quite possible that relapse and recurrence rates in patients treated in the 1970s did not apply to patients receiving treatment in the 1980's and 1990's. Our first study was a prospective longitudinal follow up of patients being treated in Cambridge in about 1990. The psychiatric services in Cambridge were fairly representative of the UK. Although it is a high powered academic center, it has an ordinary general population and the standard British National Health Service services. So we followed people with depression, from their first symptoms, every three months up to fifteen months or to earlier remission, and then for a further fifteen months to look at relapse. All subjects had major depression at inclusion and the majority had been hospitalized.

TB: What did you find?

EP: We found was good rapid remission, as we had suspected, and only a small proportion not reaching remission by fifteen months. But we then found that in the fifteen months after remission, forty percent of patients relapsed to another major episode, which was very much what earlier follow ups had found. The fact this was occurring in the 1990s did not make a difference. The strongest predictor of relapse was the occurrence of residual symptoms at the time of remission. We had set a broad criterion for remission, which allowed presence of residual symptoms rather than complete freedom; subjects who had Hamilton (seventeen item) total scores of eight or more, were responsible for a large portion of the relapses. There was a seventy-six percent relapse rate in those subjects as opposed to a twenty five percent for subjects in complete

remission. We had some data about treatment received in this naturalistic study and, as near as we could establish, neither occurrence of residual symptoms nor the occurrence of relapse were related to failure to deliver treatment; subjects with both adverse outcomes tended to receive more rather than less antidepressant. That's the way it should work in good clinical practice. Psychiatrists, being rational, give more treatment to patients doing badly. So it did not suggest failure to give treatment was the key issue.

We undertook a second study designed and targeted to collecting detailed data on the treatment actually received, subsequent to the acute episode. That had not been well studied before. There had been a number of studies, in general and psychiatric practice, showing failure to deliver good dosages of antidepressants in acute treatment, but it had not been studied beyond the acute episode. Again, ours were hospitalized depressed patients with ten percent of the sample bipolar depressives. We followed them at eighteen months after discharge and undertook a retrospective reconstruction of all treatment received and the evolution of symptoms over that period.

TB: How many patients did you have in your study?

EP: We studied a hundred subjects and the relapse rate was about the same as in the previous study. The intriguing finding was, in these severe and recurrent hospitalized patients, treatment was not seriously deficient. Compliance over the eighteen months was eighty percent of prescribed doses but about fifteen percent of the subjects declined to receive the prescription for an antidepressant. When we looked at the level of antidepressants used for continuation and maintenance they were not ideal, but there were no major deficiencies, certainly not of the magnitude to explain high relapse rates, and at eighteen months, recurrence. The major problem the study revealed was the preference of patients, in some circumstances, not to take medication. In an analysis of unmet treatment needs, we found failure to meet a medication need was, in the majority of cases, by patient refusal. When other needs for treatment were unmet, in the majority of cases they were by treatment-team inaction.

The issue of treatment acceptance is important. I had meanwhile become involved in the Defeat Depression Campaign in Britain. I was, for five years, chairman of its scientific committee and a member of the steering committee. This was a five-year campaign sponsored by the Royal College of Psychiatrists and the Royal College of General Practitioners, aimed at influencing public attitudes about recognition of depression and its treatment, as well as education of general

practitioners about treatment. We undertook three general population surveys of attitudes; at baseline, at two and a half years and at five and a half years, after the end of the campaign. At baseline, the majority of patients regarded counseling for depression as effective.

TB: What percentage of patients regarded antidepressants as effective?

EP: Only forty percent felt antidepressants were effective and seventy eight percent regarded them as potentially addictive. That explains the kind of findings when patients refuse antidepressants. We did manage to influence attitudes toward antidepressants over the course of the five-year campaign and they became about seven percent more favorable by the end of the five years. That returns me to the theme of long term outcome because with those two studies we had been considering possibilities that might explain poor outcome

TB: Where did your support for research come from?

EP: Since the mid 1980s, virtually all my work has been funded by the Medical Research Council. We had a problem group of patients who had not responded well to medications but appeared to be receiving adequate medication and for whom it might not be the full answer. We all recognize these patients in clinical practice. Patients, who only show a partial response, often have side effects and changes of antidepressant, but the right one never seems to be available. There is a possibility we still have not got the right antidepressant for everyone, so we could do with more. We looked for a different form of treatment and the one that intrigued us was cognitive therapy. There were by now follow-ups from acute controlled trials which suggested that relapse rates were lower after cognitive therapy than after antidepressant treatment. But there are possible confounding factors. Perhaps the most important is the possibility that different kinds of patients are responding to cognitive therapy and antidepressants, and these groups may have different spontaneous relapse rates. A second possibility is that in a number of studies drug continuation was not well controlled. So, we thought we had better do a controlled trial that was designed to look at relapse and recurrence and not at acute treatment. We undertook a controlled trial of cognitive therapy versus no cognitive therapy in patients with unipolar depression, who had suffered from a recent major depression which had partially remitted but showed residual Hamilton scores of eight or more and Beck Depression Inventory scores of nine or more. We wanted to ensure we were not primarily looking at undertreated patients pharmacologically, so we required all patients to be on an adequate dose of antidepressant. For the one third of patients on tricyclic antidepressants, this was a mean dose equivalent to one hundred and eighty-five

mg. per day of amitriptyline. For the two third of patients on SSRI's, the mean dose was equivalent to thirty five milligrams daily of fluoxetine, and these dosages were maintained throughout a seventeen month study. Random assignment was to drug treatment and clinical management for half the sample and to drug treatment and clinical management plus five months of cognitive therapy for the other half. This was a two-center study carried out in Cambridge and in Newcastle.

TB: Who were your collaborators?

EP: Professor Jan Scott, then in Newcastle, a psychiatrist expert in affective disorder and in cognitive therapy, and Dr. John Teasdale in Cambridge, a senior figure in the fields of cognitive therapy and mood-cognition relationships. The study commenced in the mid 1990's. The first paper on the findings was published in the Archives of General Psychiatry in September of this year, in 1999. Further papers are on the way.

TB: What did you find?

EP: A high relapse rate of forty nine percent over the seventeen months in the control group that was reduced to about twenty nine percent by cognitive therapy. All patients were taking adequate doses of medication; compliance was not affected by the cognitive therapy as it was good in both groups. Ratings were done by psychiatrists and independent raters, blind to cognitive therapy status, and we tried very hard to maintain that throughout the study. So, cognitive therapy did appear to be beneficial. Meanwhile, a small study had been published by Dr. Giovanni Fava in Bologna, using a similar, although not identical design, but a much smaller sample, which also appeared to show similar findings. We were pleased, but I don't view cognitive therapy as a substitute for antidepressants. Antidepressants are effective and do not require up to twenty therapeutic sessions. If a psychological treatment is needed, it is in patients who don't respond well to an antidepressant. And, that was essentially the finding in this study. I find myself now, in a five center collaborative study of cognitive therapy in bipolar disorder which will continue for some time to come.

TB: You have been involved in clinical research for almost 40 years. What would you consider your most important contribution?

EP: First, I think the life event studies. They were almost fortuitous and opportunistic, but they proved to be a very profitable vein which has continued and gave me my first citation classic. My heart lies in the controlled trials of antidepressants and other treatments in depression. They include the Yale-Boston continuation study with amitriptyline and psychotherapy, which was a second citation classic, and also won the Foundations Fund Prize for Psychiatry from the APA, and the second

prize from the Anna Monika Foundation. We are currently undertaking neuropsychological, PET scanning and functional MRI studies in Cambridge, to look at brain neural mechanisms underlying depression; and that is a theme which is developing nicely. Dr. Barbara Sahakian, in the Department of Psychiatry, is my principal collaborator and the leader in these studies. They are expanding considerably at the moment. But the life events work turned out well and the therapeutic trials may have done some good.

TB: Have you continued your epidemiological research in the aged?

EP: The research group goes on and is very active. It is a collaborative effort between psychiatry and epidemiology at Cambridge. We got involved in a second cohort of two thousand five hundred subjects, aged over sixty-five, from a different part of the Cambridge area, which is rural. This is part of a large-scale national study and is also linked to brain banking. I have progressively withdrawn from those studies, but I am still a member of the groups.

TB: You published many papers during the past decades. Could you say something about your first publication?

EP: My first publication was a letter to the editor of the British Medical Journal describing a patient who received a combination of methyldopa, an antihypertensive which is no longer used, and pargyline, that we now know to be an MAO B inhibitor. She had been treated by her general practitioner with both these drugs and had developed vivid visual hallucinations, apparently with clear consciousness.

TB: When was it published?

EP: In 1966.

TB: Could you say something about your last publication so far?

EP: Well, I now find it difficult to keep up, because what was the last publication last month is no longer the last publication this month. I suppose the last major publication was the cognitive therapy trial in September, but there have been about four more coming from our neuropsychological and other work. So, it goes on.

TB: You had a couple of citation classics. Any of your other work you think has had influence?

EP: The other work that has had influence was the continuation therapy study, and the work on general practice depression has had considerable influence, particularly in Britain, on the use of antidepressants in general practice. In the life events work I am still asked to write reviews and our Interview for Recent Life Events is used widely by other groups. It is an area that we build into other studies. The naturalistic first follow-up study of depression in Cambridge also involved looking

at life events, social support, marital relationships, expressed emotion, and their relationship to relapse. In that sample of severe and recurring depressives, life stress tends to fade into the background. Life events are of major importance in first episodes and perhaps second and third episodes but with recurring episodes depression becomes more autonomous.

TB: In addition to research could you say something about your other activities?

EP: I am chairman of a department, which, although not large by American standards, is moderately sized by British standards and growing rapidly, so I have to look after that. That involves the usual mix of medical school and hospital activities as well as building our research reputation; we are one of the best-rated departments in Britain for research, which is very important in the Cambridge environment. In the national research assessments of all university departments, which, takes place every few years, we have been in the very top group consistently. Then there are other University activities. I am fortunate to be a member of the Syndicate of Cambridge University Press. The Syndicate oversees the activities of this very large university academic press. As a bookish man, being a member of the Syndicate has been a great pleasure to me.

TB: Am I correct that you were the founding editor of the Journal of Affective Disorders?

EP: I was indeed. George Winokur and I founded it in 1979, and we got great pleasure in watching it succeed. Then I was asked if I would be prepared to become editor of Psychological Medicine, a larger journal published by Cambridge University Press The journal was founded and edited by Michael Shepherd and he was retiring. It is a major international journal across the broad spectrum of psychiatric research. Ultimately I agreed to take it on and I have continued to be its editor from 1994 on, leaving the journal of Affective Disorders at the same time.

TB: What about your clinical activities?

EP: In the hospital, I lead a small resistant affective disorders specialist unit, with a therapeutic team to help me. My personal clinical work is limited though, by lack of time.

TB: Any other university related activities?

EP: In the university, I am a Fellow of an ancient Cambridge College, Gonville and Caius College. Cambridge life is complex; we are all members or Fellows of a College, as well as of departments. I wasn't a Cambridge man, far from it, and I felt very fortunate to become a Fellow of this

ancient college. Francis Crick, of the double helix, was a Fellow there, but has lived in the USA for many years. Sir Ronald Fisher, the father of modern statistics and analysis of variance, was a Fellow there many years ago. Stephen Hawking is a star, today.

TB: You have been a member of several professional organizations.

EP: I have been a long-time member of psychopharmacological organizations. I like joining things. As a young American researcher, I became a scientific associate of the ACNP in the late 1960's. After returning to the UK, I ceased to be eligible but I was fortunate to become a foreign corresponding member later. I first went to a CINP meeting in 1970 in Prague, and that was a very seminal meeting, which certainly had an enormous effect on me. My wife was pregnant with our first American citizen child and also came. It was a sad time in Czechoslovakia after the ending of the liberalization of the Prague spring, with Soviet tanks outside the city. I have been a regular member and attendee of CINP congresses ever since and suffer for my crimes by being president-elect, something I feel is a great privilege. I was an early member of the British Association for Psychopharmacology, the BAP, its president many years ago and now an honorary member. At one stage, I was very active in the Royal College of Psychiatrists and became its Vice President. I was also President of the Marce Society, the international association concerned with psychiatric disorders of childbearing.

TB: You have been very much involved in teaching and training.

EP: Yes!

TB: Would you like to mention some of the people you trained?

EP: I have been lucky, as I have had very talented younger collaborators. Of the people from my time at St. George's several have now become professors, including Professor Cornelius Katona, who is a professor of the University College, London and Dean of the Royal College of Psychiatrists, Professor Thomas Barnes, an eminent psychopharmacologist in schizophrenia, Tony Hale also a psychopharmacologist, and Ted Dinan, who was the professor at Barts and is now Professor of Psychiatry in the medical school at the Royal College of Surgeons in Dublin, Ireland. In Cambridge, David Healy, has emerged as a historian of psychopharmacology like yourself, and is one of your collaborators. He is a young man with immense creativity. Now there is a group of younger people in Cambridge who are traveling the same route.

TB: In addition to papers you have also published a few books.

EP: I believe it would be eight books and I think now we are up to three hundred and four papers and chapters.

TB: Would you like to say something about your books?

EP: My first book was written with Myrna Weissman, out of our Yale work and was called *The Depressed Woman*, published by University of Chicago Press. This was a study of the social relationships, measured by our Social Adjustment Scale, in a sample of depressed women from our therapeutic trial and a sample of matched controls from the general population. My second book was a British Association for Psychopharmacology Monograph, edited with Alec Coppen, and called *Psychopharmacology of Affective Disorders*. It tells you where I stand. A major undertaking was the *Handbook of Affective Disorders*, first edition in 1982, and second edition in 1992.

TB: Was it translated?

EP: Well, the Handbook was translated into Spanish, and widely used in South America. All the time, I have had this balance between psychopharmacology and biological psychiatry on the one hand and social psychiatry on the other. That's because I think they are both important and because I have enjoyed both. So the most recent book, published a few years ago, was an attempt to look at the role of prevention in psychiatry. That again was an edited book, with Professor Rachel Jenkins, a British psychiatrist, now a professor at the Maudsley, who has been a very influential figure within the government department responsible for our psychiatric services, the Department of Health. We tried to be cautious, but to be authoritative and also point to a few future directions for prevention in psychiatry. We concluded that it would be unwise to invest large sums of money in psychiatric prevention yet and that well-evaluated pilot projects were needed. In the long run a mature branch of medicine has to have preventative techniques.

TB: Any new book coming?

EP: I have no new books coming, as books take a long time and currently my life is too busy to fit them in. I have been putting what little time and effort I have for publishing, into both editing a journal, and writing papers.

TB: Do you have any private practice?

EP: No, in the British tradition academics do not usually undertake private practice, although, that is slowly changing. But, as a man who works all hours of the day and night and is fortunate to have a family who have permitted that, I don't think it would be fair to anyone, including patients, to be seeing private patients.

TB: But as I understood it you are still seeing patients on your Unit.

EP: I also, every week, undertake a ward round on my inpatient unit, which is a detailed review of patients and deciding about their treatment,

and every week I have an outpatient clinic in which I see one patient who invariably is a second opinion referral from another psychiatrist in Cambridge or from further afield. This week it was a patient from New York with resistant affective disorder.

TB: You have given several prestigious lectures.

EP: I was the annual guest lecturer some years ago for the ACNP and, as you might guess, I spoke about antidepressants. I have been the annual guest lecturer for the BAP, talking about a similar theme. I have been the Maudsley Lecturer of the Royal College of Psychiatrists, which is the senior lecture of the Royal College. I was talking about the treatment of depression more broadly. And, this year, in March, I was the Gerald Klerman Memorial Lecturer at Cornell University Department of Psychiatry, describing our more recent work. Next year in April, I will be giving the first memorial lecture for someone who was a very dear friend and that's Brigitte Prusoff at Yale, who was the statistician whom I collaborated with for many years and one of the most helpful people I have had the privilege to know.

TB: Is there anyone else you would like to mention of people you collaborated with or who had a major impact on your career?

EP: I have mentioned a number of names over the course of this interview, such as Myrna Weissman. We were research siblings and collaborators, and have been friends over many years. Of the senior figures who taught me and influenced me there were many. It's difficult to select people out, because, if one has any sense, one learns from everybody. It seems to me that, constantly throughout life, I had to learn new things because of demands my career and increasing age put on me. I have always done my best to learn from those around me, senior, contemporary and younger. Nowadays, the young psychiatrists know so much more neurobiology than I ever learned. Much of it wasn't even known when I was a student.

TB: Is there anything we left out and you would like to add?

EP: On a personal side, yes. I grew up in a musical family. My mother kept active as a pianist throughout my childhood and adolescence in New Zealand. I learned the violin but I have a poor ear and gave it up. My two sisters are both musicians. One, living in England longer than I have been, was a flautist, a teacher of the flute and married to a professional violinist, so their life has been music. The other one in New Zealand is a cello teacher. I love listening to music, but my service to music is not to perform it. My wife was a librarian at the Maudsley when I met her. In later years, she has become a textile artist, very creative with a brilliant sense of color. Both she and I are very keen on music,

theater, and opera. But we both have become so busy there is much less of that in our lives than there used to be. We have two adult sons of whom we are proud.

TB: On this note we conclude the interview with Professor Paykel. Thank you, Gene for sharing this information with us.

EP: Thank you.

FREDERIC QUITKIN

Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December 11, 2001

TB: This will be an interview with Frederic Quitkin* for ACNP's archives. We are at the annual meeting of the College in Hawaii. It is December 11, 2001. I'm Thomas Ban. Let us start from the very beginning; where and when were you born. Tell us something about your early interests, education and how you got involved in the field.

FQ: I was born in Brooklyn into a middle class family, which had intellectual interests. My father was the product of the depression, so he didn't have an opportunity to do everything in education he would have liked. This was also true of my mother. My father was a real intellectual. My mother was also, but to a lesser extent. My father instilled the idea of doing research into me in a rather subtle fashion.

TB: Where did you go to university?

FQ: I was fortunate enough to get a scholarship to Princeton, which was a wonderful experience. It's a great university. Unlike other universities, undergraduates are required to write a thesis. As biology major, I had to do a project to do with the effects of urethane analogs on viruses. I then went to medical school at Downstate. I had, without knowing anything about it, an interest in psychology and perhaps psychoanalysis. But I went to medical school and my first interest first in pathology, which I got tired of, then internal medicine and finally, psychiatry. I decided routine cases in internal medicine would not be as interesting as routine cases in psychiatry. I went into psychiatry thinking that I would be a psychotherapist.

TB: When and where did you do your residency?

FQ: In 1963, I started at Hillside Hospital, where I was fortunate to meet Don Klein. I very quickly became disillusioned with psychoanalysis and felt that there was no empirical base to it. "Freud said it, so you should believe it," was the spirit at Hillside in the 1960s. Then I was exposed to the empirically-based research Don Klein was doing and developed an interest in psychopharmacology.

TB: Didn't you get involved in research as a resident?

FQ: That's true. I got involved in research and I did a couple of studies.

TB: What did you do?

FQ: At the time, virtually all inpatients were diagnosed as schizophrenic. So one of the studies I did as a resident was a follow-up of a patient

---

* Frederic Quitkin was born in Brooklyn, New York, New York in 1937. Quitkin died in 2005.

who had been suicidal for a year. After she was transferred to a State Hospital she suddenly got better and left in 2 weeks. So I planned a study Don Klein helped me with. He re-diagnosed everybody transferred from Hillside, which was a comfortable, pleasant place to be treated, to the State Hospital. The hypothesis was that the non-schizophrenics would quickly leave the State Hospital whereas the schizophrenics he diagnosed would stay. The prediction was right. Clinicians labeled virtually all patients schizophrenic so this had no predictive value.

TB: What did you do after your residency?

FQ: I went to a Doctor of Medical Science program run by an experimental psychologist, Dr. H. Witkin, at Downstate Medical Center. It primarily consisted of courses in how to do research. I had exposure to statistics and design, and, in 1969, I went back to Hillside and got involved in psychopharmacologic research. There were three broad themes. The first theme consisted of studies involving the maintenance and prophylactic treatment of schizophrenic and bipolar patients. It was when lithium first came out. I was also interested in neurological signs of schizophrenia.

TB: What about the second theme?

FQ: After moving to Columbia in 1977 I became interested in two areas; atypical depression and placebo response. Using the response to antidepressants we showed that atypical depression did better on monoamine oxidase inhibitors (MAOIs) compared to melancholic patients, who did well on either tricyclic antidepressants (TCAs) or MAOIs. Our findings indicated a categorical distinction between the two diagnostic groups. Subsequent epidemiological genetic studies by others suggest atypical depression may be distinct genetically from melancholia.

TB: Tell us something about your research with placebo.

FQ: I was involved in identifying those with placebo responses to drugs. Sixty percent of depressed patients improve on a drug and thirty percent on placebo. The question was to identify characteristics of patients who got better on placebo. We found if you got better in the first two weeks or had a fluctuating response, you probably were having a placebo response. The big difference was that improvement in the drug group occurred after the third week and later. It was convincing to see that those with a placebo pattern, randomized to drug or placebo, did well on either whereas for those with a "specific drug response," did better on drug than those randomized to placebo. We published the findings in the Archives a few years ago. In another study with Remeron (mirtazapine) we virtually replicated our prior findings.

TB: What about the third theme?

FQ: I was interested in the relationship of substance abuse, mood disorders, and self-medication. So I did several studies in this area and have shown that patients who had primary mood disorders and received antidepressants versus those who got placebo did better in terms of the way they felt and their substance abuse diminished. We did a similar study with outpatient alcoholics.

TB: What else did you do at Columbia ?

FQ: I ran a depression clinic where we were fortunate to admit only people who were willing to go into a study in exchange for treatment for six months. During my stay at Columbia I have focused entirely on research in depressive illness.

TB: Wasn't your first research project at Columbia focused on the differentiation between atypical and other depressions?

FQ: That study went on for about 10 years. There were multiple different trials to be sure our findings are correct. We used our own criteria for atypical depression, which became the basis for a parenthetical modifier in the DSM-IV.

TB: Did your findings in atypical depression differ from the findings of William Sargent in the UK?

FQ: Sargent never spelled out his criteria. The prevailing opinion in the UK. was that it was anxious depressives who did better on MAO inhibitors. We analyzed our data and showed it made no difference whether the patients were anxious or not. Patients with reversed vegetative symptoms, even in the absence of anxiety, have a big difference in treatment response between MAOI and placebo.

TB: Didn't you publish on the prophylactic treatment of schizophrenia at Hillside?

FQ: I did studies on prophylactic treatment with phenothiazines in schizophrenia. I probably had 30 publications before I went to Columbia, perhaps 40. I had a wonderful close collaboration at Hillside with Arthur Rifkin.

TB: Could you elaborate on your findings on prophylactic treatment with phenothiazines in schizophrenia?

FQ: The drugs made a big difference, which was the bottom line.

TB: What was your latest publication?

FQ: A paper in which I evaluated the work of Fisher and Greenberg when they say that double-blind studies are not double-blind because guesses exceed chance.

TB: You have been working with Don Klein your entire research career.

FQ: I am extremely fortunate to have worked with Don Klein. He was always fair and an inspirational model and we had very good support

at Hillside. The medical director liked research. Being at the New York State Psychiatric Institute was a stroke of luck, because we didn't have to worry about soft money and were given a lot of options. So I deem myself blessed. I try not to depend too much on drug companies, and to keep opportunities for my intellectual curiosity.

TB: Is there any particular drug you found more interesting than the others?

FQ: I don't think that there are differences between the drugs produced in 1958 and the new ones. The new ones are more user-friendly but, in terms of efficacy, I don't think one is better than another. The main difference with antidepressants is how people tolerate them, which is unpredictable. They are approximately equally effective, although there is an advantage in atypical depression with MAO inhibitors. However, MAOIs are no longer first-line drugs.

TB: In addition to many papers didn't you publish a book?

FQ: I wrote a book with Don Klein, Rachelle Klein and Arthur Rifkin. It was a lot of work, but I learned a lot.

TB: At the time you entered the field there were very few psychotropic drugs available, primarily phenothiazines.

FQ: You are right. When I started, around 1963, there were only a very few psychotropic drugs. We've made enormous progress.

TB: Would you like to talk about people you worked with?

FQ: I have been extremely fortunate in that I've always worked with people I had collegial relationships with. First, with Arthur Rifkin and John Kane, who I still have a good relationship with. When I went to Columbia, I began working with Jonathan Stewart, Pat McGrath, and Ned Nunes. I've had relationships with colleagues who I trust, who're very bright, and hard working. A lot of things fell into place. I view myself as extremely fortunate in that respect.

TB: Is there anything else you would like to mention?

FQ: We hit on most of the things. It's been a lot of fun. I wouldn't mind doing it for another 40 years.

TB: Are you still fully active?

FQ: Absolutely. The best is yet to come!

TB: That's very good. Well, thank you very much, Fred.

FQ: Thank you.

ALLEN RASKIN

Interviewed by Leo E. Hollister
Washington DC, April 17, 1997

LH: It is 1997 and we are in Washington, DC recording another videotaped interview concerned with the early history of psychopharmacology. This is the series sponsored by the American College of Neuropsychopharmacology. I am Leo Hollister and I have as my guest today, Allen Raskin,* who has been around psychopharmacology for a long time. Welcome aboard!

AR: Thank you, Leo.

LH: It is always interesting to know how people got started in their field so what impelled you to become a psychologist and how did you got involved with psychotherapeutic drugs.

AR: I'm not sure what impelled me to become a psychologist except I got good grades in psychology in college. So, I decided I would continue.

LH: Really!

AR: I got my degree in clinical psychology at the University of Illinois. Illinois was characterized at the time for being a haven for dust bowl empiricism and had a strong emphasis on research and statistics. And, some of that rubbed off. When I left Illinois I went to the VA for a few years as a staff psychologist. Then I was fortunate to get a job with Maury Lorr doing psychotherapy research in Washington DC.

LH: You were still with the VA?

AR: Right, because Maury was with the VA. We were doing collaborative outpatient studies and looking at psychotherapy. Whether twice a week was better than once a week or once a month. It turned out frequency was not the critical variable but staying in treatment was.

LH: You mean the total duration?

AR: The total duration you remained in treatment. There was a comparable group you were involved with. It included Jack Lasky and the group at the Perry Point VA Hospital doing collaborative drug trials with schizophrenic patients. Others included Jim Klett, John Overall and Gill Honigfeld.

LH: Well, yes.

AR: We would all meet annually in Cincinnati, sort of the middle of the country. Maury started getting involved in drug trials while I was there. He looked at chlordiazepoxide (Librium) at one point. Mostly the interest of our group was in reducing anxiety in psychotherapy patients, the notion

* Allen Raskin was born in Brooklyn, New York in 1926.

being if you could get anxiety to a reasonable level it would facilitate psychotherapy.

LH: Psychotherapy?

AR: Yes, right, that's sort of ironic. My memory may not be accurate, but my recollection is the last project I was involved in with Maury was called, *Chlordiazepoxide as an Adjunct to Psychotherapy*. But, that was a very good experience for me. You said you didn't know Maury, then, or were you not sure?

LH: I first ran into to Maury when the VA Cooperative Studies were being done in the late 1950's. I think 1958 or 1959

AR: He was a great mentor; a very capable statistician so a lot of my interest in instrument development began with him. He did the IMPS (Inpatient Multidimensional Scales). The BPRS (Brief Psychiatric Rating Scale) evolved from the IMPS.

LH: I remember when the IMPS was all we had.

AR: Then John Overall created the BPRS. When I left Maury, I went to DC General Hospital and was working on a project that Sol Goldberg was coordinating. That was one of the first multi-site trials the Psychopharmacology Service Center (PSC) got involved with, a drug trial with schizophrenic patients. The drugs were chlorpromazine and placebo and I was a Co-Principal Investigator. That was an eye opener because DC General, at that time, had very acute psychotic patients who were climbing the walls, doing all kinds of things. They were giving 25 and 50 milligrams a day of chlorpromazine but when we came we were using 600 mg. a day and getting some very interesting results. It was a whole different thing.

LH: What year are we talking about?

AR: 1960 or something like that. At the end of my stay, I was invited to the PSC that was to become the Psychopharmacology Research Branch (PRB.) Jon Cole was the director and I was hired by Sol Goldberg who knew my work over at DC General. They were looking for someone to do a collaborative depression project. That was a ten-hospital study in hospitalized patients.

LH: That came after the ten-hospital schizophrenia study. .

AR: Right. So, there was an interesting aspect to that. The original intent was to compare chlorpromazine with imipramine and a placebo. Max Fink was on our review group at that time and had done a trial with chlorpromazine in depression. I think it was done with Don Klein, as a matter of fact. Well, he was pushing the combination of chlorpromazine and procyclidine rather than chlorpromazine alone. So, we took a time out and for a year looked at the combination versus chlorpromazine

alone, to see whether there was a difference. The results showed the combination was no more effective so we opted to go with chlorpromazine alone.

LH: Didn't the procyclidine reduce the number of extrapyramidal signs?

AR: Yes, but it didn't have a great impact on depression. So we started the ten hospital trial that ended up with 500 patients.

LH: Will you review that trial?

AR: These were hospitalized depressed patients that came from both rural and urban hospitals nationwide. We were in Rochester, Minnesota and Sheppard Pratt in Baltimore. It was an interesting group, because we had one hospital, Hartford Hospital, where the average patient stayed about ten days and this was years before managed care. At Sheppard Pratt when you admitted the patient they asked relatives if they had brought seasonal changes of clothing. So, we had this wide range of settings which was one of the variables we looked at, and it made some difference. The drugs were imipramine 300 mgs. a day, chlorpromazine 600 mgs. a day and placebo. We were focusing on drug effects in patient subtypes; the idea of the "right drug for the right patient". John Overall was invested in that and I guess you were also.

LH: Everybody took a crack at that and nobody ever hit it.

AR: Right! One of the groups we looked at was John Overall's three types, the hostile, the anxious, and the withdrawn-retarded depression. The retarded did best on imipramine, so that fit with expectations. The anxious did show some beneficial effects on chlorpromazine, so there were some differential effects. We also looked at the endogenous-neurotic distinction and patients with psychotic and neurotic diagnoses. The psychotic patients did better on imipramine. Other people have had different results, but the neurotic patients in our study did reasonably well on placebo. I also looked at age and gender but don't remember if there was anything else. It was the subtype issue that was of major interest in the study. Of course, imipramine was an effective treatment but it was only a six-week trial. The seventh week patients were off meds. Patients on chloropromazine showed improvement in the withdrawn retarded area, when taken off. That study was my first major entry into psychopharmacology.

LH: When was that published?

AR: 1971. This study generated a lot of articles because I had so much data to deal with.

LH: Later, I seem to remember you were involved with a study of anxious patients?

AR: At or toward the end of my stay at the branch. My next incarnation was with elderly patients when I did a hyperbaric oxygen study in patients with dementia. That's one I feel good about, because it was a replication study with controls. The original study was done by Eleanor Jacobs, who was a psychologist at the Buffalo VA Hospital and she reported that hyperbaric oxygen was tapping into brain cells dying because of a lack of oxygen. I subsequently learned there's a "ceiling" phenomenon which prevents oxygen getting into the brain beyond a certain point, but these patients about $7000, for treatment and social security was providing the money. That study also provided a boon to Bethlehem Steel, who manufactured the hyperbaric chambers.

LH: Oh, Lord.

AR: I was mandated to do the study because of its economic importance and it was with Sam Gershon in New York City, using the hyperbaric chamber at the Rusk Rehabilitation Medical Center. We had hyperbaric air, which was a nitrogen-oxygen mixture and hyperbaric oxygen. We also had normobaric, ground level, oxygen and normobaric air. The results were interesting; we didn't show a benefit for hyperbaric oxygen over hyperbaric air, but we did show a "Western Electric" effect; people who went into the chamber, whether they got air or oxygen, seemed to do a little better than those who didn't. We attributed this to the mystique of the chamber.

LH: That's pretty impressive. It would have made me anxious.

AR: Maybe we should just put people in the chamber for an hour and then let them out!

LH: This was done under the auspices of the PRB?

AR: Right. We had a grant application from NYU, with Sam Gershon. Steve Ferris was hired to coordinate the study. Steve has since made a name for himself working with the elderly. Barry Reisberg was also brought in to work on this trial and the study had to pass through the review panel.

LH: If I recall you were also testing imipramine, a benzodiazpene and placebo in anxious patients?

AR: Imipramine? We did one study where we looked at phenelzine, diazepam and a placebo in depressed patients.

LH: I'm probably wrong.

AR: The effects were not nearly as striking as the effects of imipramine had been in the prior trial. This was the same group of 10 hospitals as in the original imipramine vs. chlorpromazine study. I did get involved in the anxiety area in a funny way. I don't know if you knew of the controversy Don Klein was having with Isaac Marks on the relative benefits of drugs and psychotherapy in anxious patients.

LH: It's still going on.
AR: Yes, right, it hasn't stopped. I had access to some data Isaac had collected. The question was if I reanalyzed that data would I get the same results that he got. Don was of interested in that so I made the mistake of doing it, and I didn't get the same results.
LH: Well, there was no reason they both couldn't be right.
AR: You are right, but Don still comes up to me every once in a while and wants me to publish those findings in a journal, although I've already referred to them in a chapter.
LH: Don has been a very creative thinker, but I have doubts he could identify a new class of anxiety by the response to drugs. Who could do anything in a logical fashion just based on the response to the drug, because the drugs are far less specific than their names imply? So that brings you up to the 1980's?
AR: Can I back track?
LH: Of course!
AR: If I have any sort of a reputation in the field it's in instrument development, including the Raskin Scale, which was picked up by the drug companies.
LH: Did that scale stem from your work with Maury?
AR: No, but other rating scales I developed did. The Raskin Scale was developed for use in the ten-hospital collaborative depression study. Most investigators, up to that time, entered patients into a trial in terms of diagnostic criteria. They were not tapping into the intensity of symptoms. My scale was a crude effort to provide an entry screen, where you had a score of at least nine on three five point rating scales measuring severity of symptoms in verbal report, behavior and secondary symptoms of depression.
LH: What's the official name of it?
AR: I called it the Three Areas Severity of Depression Scale but it became known as the Raskin Scale.
LH: So this was one of the first studies to put a barrier up to ensure a certain level of psychopatholgy before entry?
AR: Right, it's like the HAM-D now. I never intended it as a change measure; it wasn't designed for that. But the drug companies adopted it as a change measure. Jon Cole used to talk about a rating scale being "quick and dirty," so this three item scale appealed to some investigators. It became very popular and was used in many drug company depression trials. We also had other rating scales in this study that measured a wide range of symptoms and some of were outgrowths of the IMPS and other scales.

LH: At that time there were a great many searches for rating devices to capture parts of psychopathology. We started to develop a depression scale and reviewed the literature to find there were already thirty-five different scales.

AR: I'll tell you a funny story. Max Hamilton was on a year sabbatical at St. Elizabeths Hospital when he was developing the Hamilton Depression Scale. He used to come up and see Maury and our group to have little chats about it.

LH: Max was an interesting person. He was somewhat compulsive. I guess his scale was next in popularity to the BPRS and has retained its popularity longer than any other.

AR: That's right.

LH: We got to about the 1980s now. What have you been doing for the last fifteen years?

AR: I left the PRB in 1985, took retirement and went to Detroit to work at the Lafayette Clinic with Sam Gershon for a few years. We were trying to evaluate adolescents with suicide attempts and what reasons were behind the attempts. That was subsequently published and showed that most adolescent suicide attempters were young girls and the attempts related to problems with boy friends. Unfortunately, many attempted suicide by taking large doses of Tylenol which can destroy the liver. I am currently working at the University of Maryland but my research is at Perry Point.

LH: Back home!

AR: Right. But the staff at Perry Point has no awareness of all that went on when the BPRS was developed and the collaborative study group was there. That memory has disappeared.

LH: That's one of the reasons we are doing these interviews; to make sure they don't disappear. All those studies were done thirty years ago and no one has any memories of the past. I think this is due to the fact when you tap into a computer to look up references they don't go back very far.

AR: No, they only go back about ten years.

LH: Anything that happened before then is like it didn't happen at all.

AR: Right. I did some work on race differences in terms of drug response that is now coming back. Using data from the collaborative depression study we looked at age and gender differences. Those things were done but are not referenced anymore because they go back beyond the ten-year period. I am now serving as a mentor for the Geropsychiatry Fellowship program at the Psychiatry Department at University of Maryland. That's my current thing.

LH: What's that about?

AR: These psychiatrists are required to have a research experience in a fellowship after residency. The American Psychiatric Association awards an Advance Degree in Geropsychiatry and one of the requirements is a research experience. That has given us a better opportunity to recruit psychiatry fellows. When I first came about nine years ago I was involved with Jerry Levine and a young psychiatrist named Larry Alphs. He was in the process of developing a negative symptoms assessment scale. We followed up on that and collected data on 100 schizophrenic patients at Perry Point. I factor analyzed that data and we published the results. I am not convinced there are drugs that are effective for negative symptoms in schizophrenia.

LH: You mean that there are no drugs that are specifically good for negative symptoms?

AR: I'm not sure there are. I know Herb Meltzer has been working along those lines.

LH: I used to tell a story about negative symptoms and traditional antipsychotic drugs when we first started using chlorpromazine and I spread it around to a number of wards. I remember calling up one of my good friends and asking, "Wally, would you like to get some more patients on chlorpromazine?" He replied, "Leo, I have so many patients talking to me now who never talked to me before so this is all I can handle". If that is not reversing negative symptoms, I don't know what is. Where does all this doubt come from?

AR: I have a different experience. These patients are all talking, but their initiative is gone I have been working lately with chronic schizophrenics in community residences. The VA, Perry Point, has a program with about 200 patients.

LH: So, you are saying they are burned out.

AR: Yes, they talk to you, but the level of activity and everything else is gone.

LH: The term "burned out schizophrenic" has been around for several years. But that's different from the presence of positive and negative symptoms. Some years ago I looked over some rough data John Overall and I collected over the years, and his scales can be factored into positive and negative elements. It looked as if negative symptoms improved in parallel with the positives, only not as much. They were improving but didn't achieve as big a change as the positives. I guess that's an issue I am in a minority on.

AR: The burned out patients may be a whole different thing. We have done a variety of other things. We have looked at Vitamin E for tardive

dyskinesia. We didn't find any important or significant effects for over a year. Lately I have been working with a neurologist on a dementia unit at Perry Point who has some ideas about screening tests to distinguish Alzheimer's from multi-infarct patients. I'm not terribly impressed with our findings but it's one of the other areas I've been working on.

LH: In the old days we thought most things were vascular in the dementias of older people but, in the last fifteen to twenty years, it has swung over to Alzheimer's. You hardly ever hear anything about vascular dementia anymore although it's beginning to come back and people are realizing what neuropathologists did a long time ago, the pathology can be mixed and a sizable number can have both.

AR: I worked with a psychiatrist in a nursing home in New York City. He was able to get permission to autopsy patients and we collected some data. These confirmed what you are saying; when he looked at the brains they were mostly mixed.

LH: I remember the neuropathologist at the Langley Porter Clinic, who probably saw more brains of mental patients than almost any neuropathologist around. He reported that perhaps 35 to 40 percent were mixed and he couldn't make a distinction. Its funny how fashion in diagnosis changes. I remember the first study we did with Hydergine in what I then called senile psychosis associated with old age. I found no effect except in patients who had what was then called hypertensive brain disease, essentially vascular dementia. That's what you would expect with Hydergine.

AR: I thought it had a little effect in depressed patients with Alzheimer's. Gerri Schwartz conducted a trial with Hydergine for the drug company. She developed a scale used in geriatrics that was rated by relatives. I am finishing up a drug trial with physostigmine for Alzheimer patients these days.

LH: Are you using the slow release form?

AR: Yes; the oral slow release form. I didn't break the blind yet, but Forrest Laboratories hopes it may have beneficial effects.

LH: Well, it makes sense. Of course, ever since physostigmine came out for use in dementia in the early 1970's people had been looking at it. When Ken Davis was with me we did some studies with it, but it's tricky; you have to find the right dose and if you overshoot that skews your results.

AR: That's an area crying out for effective treatment.

LH: Hurry, hurry! Every time I can't remember a name, I begin to worry.

AR: I am running out of steam. Do you have any other thoughts?

LH: We may have covered all we need to. Your interests have been very varied over the years.

AR: I kid myself and say I'm a renaissance man, because I've been in every area of psychopathology. Something else I did I think is interesting; I served as editor of the Psychopharmacology Bulletin after Alice Leeds.
LH: She was a character wasn't she?
AR: Yes, she was. She built up the international aspect of the Bulletin in a big way.
LH: Yes, the Pharmacology Bulletin still appears.
AR: When I was there we were under the gun; it was one of those times when the federal budget was being heavily cut. I became very adept at writing memos to everybody, trying to justify keeping the Bulletin in existence. That was a nice experience once I overcame the anxiety of keeping it going. One of the things about the Bulletin was the quick turn around. If something was presented at a meeting you would see it in print in a fairly short time.
LH: A lot of your material came from the NCDEU.
AR: Also the ACNP for a while, but now they have cut that out.
LH: Then there was the Schizophrenia Bulletin.
AR: And, the beautiful pictures on the cover, paintings by schizophrenic patients. In the Psychopharmacology Bulletin we did special editions and that was fun. We had a special edition on pediatric psychopharmacology and Judy Rappaport was the editor. I did one about rating scales for geriatric patients.
LH: Didn't Steve Ferris come up with a rating scale for geriatric disorders?
AR: Barry Reisberg, who works with Steve, is the one who developed those scales.
LH: One of the most impressive developments in neuroscience is the greater understanding of Alzheimer's that has come about in the last ten years.
AR: My wife can always tell when I have been over working on the Alzheimer's project. I come back with this very depressed aura, having talked to the relatives.
LH: It's an awesome burden and such a tragedy to see productive people reduced to infancy almost.
AR: There was one man we had in our project who had been the head of the geography department at a large university and his wife says he gets lost just going out the door now.
LH: It's very sad to see someone like Ronald Reagan go through this. What a way to terminate a successful four years. You can't help but feel sympathetic toward his fight.
AR: I have enjoyed this. Thank you.
LH: Thank you for coming by and doing this interview.

KARL RICKELS

Interviewed by David Healy
San Juan, Puerto Rico, December 14, 1998

DH: My name is David Healy. Today is Monday, the 14th of December 1998. This is an interview with Karl Rickels* on behalf of ACNP at the Annual Meeting in Puerto Rico. Karl, can we begin with where you were born?

KR: I was born in Germany; grew up in Berlin; became a prisoner of war in Africa; spent time as a prisoner of war in the USA; returned to Germany in 1946, and went to medical school in Munster, West Germany.

DH: Did it take you four or five years to go through medical school?

KR: Five years.

DH: Often after the war, it took less than five years as they were trying to get people through quickly. At the time you went to medical school, did you have any thought you might do psychiatry?

KR: I didn't know anything about psychiatry. I was planning to go into public health and pathology. After my internship I started residency in bacteriology and microbiology. But I always wanted to go to the States, having been in a prisoner of war there.

DH: Why?

KR: I had a great time in the States. I was treated very well. I enjoyed the country. There was freedom of ideas and I always wanted to return. When I saw an ad for a job in a mental hospital in Iowa. I applied and was accepted in 1954. That was my first contact with psychiatry. I spent a year at the mental hospital in Cherokee, Iowa, where they were still doing lobotomies.

DH: This was just before chlorpromazine?

KR: It was a state hospital. They used transorbital lobotomy to calm very violent patients and physical restraints to control those who were excited and agitated. While I was there a few patients were started on reserpine and Thorazine (chlorpromazine.)

DH: Which of the two did you get first?

KR: I think we had reserpine.

DH: What was the impact of the introduction of drugs? Do you have any memories of the first patients you saw treated with them?

KR: Well, we used them primarily to calm people down. We didn't know what they would do long term. But they certainly produced calmness and controlled patients on the wards.

---

* Karl Rickels was born in Wilhelmshaven, Germany in 1924.

DH: It must have been very noisy, smelly and dirty on the wards in those years.

KR: Yes, in the beginning. Still, I decided to enter psychiatry and get a good training. So, I contacted a few places on the East Coast and the University of Pennsylvania asked me to visit but I didn't have enough money to travel. They interviewed me by telephone and I was accepted. After one year at the state hospital, I moved to Penn

DH: What was the orientation of psychiatry there?

KR: It was pretty much psychoanalytic. I finished my residency in 1957 but stayed in the department and worked in the outpatient clinic with patients who at the time were referred to as neurotics. I became interested in anxiety disorders and outpatient depression, and especially on the effect of non-specific factors on drug treatment. My research has been supported since 1959 by NIMH.

DH: What kind of patients did you get at the outpatient clinic in those years?

KR: In my first outpatient study we compared phenobarb with meprobamate. It was not done at the psychiatric outpatient clinic because that was too psychoanalytic. I had to go to the medical clinic to find patients for my research.

DH: You mentioned in your first study you used meprobamate.

KR: It was the first tranquilizer that was a little bit better than the barbiturates. It was the best tranquilizer until the benzodiazepines, Librium (chlordiazepoxide) and Valium (diazepam) came along. Then, in 1961, Sy Fisher, E. H. Uhlenhuth and I started the first outpatient collaborative study with psychotropic drugs supported by NIMH. It was focused on non-specific factors that might have an effect on treatment response. It was carried out at Hopkins and Penn. We demonstrated, for example, the effect of doctors' attitude on the outcome of treatment. We also studied whether side effects can be manipulated by non-specific factors. It was interesting to learn that many patients interpreted sedation as a positive, and not a negative event.

DH: Where did you get the idea to look at these kinds of interactions? Did you have any contact with Beecher?

KR: I published a book following the 1966 World Congress of Psychiatry in Madrid to which Beecher added a chapter and I became interested in this area of research because I felt that we didn't have sufficiently powerful drugs for treating the disorders I saw.

DH: That line of thinking has been lost, hasn't it?

KR: It has been lost but to some extent is being rediscovered. Medline only goes back to 1966, and some of the findings in this area of research were published before that, in the late 1950s and early'60s.

DH: Recognition that drug therapy is influenced by the attitude of the physician towards treatment; that a patient's interpretation of side effects can substantially change the outcome of treatment. Those are not the kind of things anyone can put into a pill and market.

KR: A physician who gives a drug but doesn't spend time with the patient usually doesn't get as good results with the same medication as the physician who does. Our interest was learning more about the psychological underpinning of drug response in anxiety disorders. At the time there was also interest in trying to improve the methodology of clinical investigations because it was no longer only the safety but also the efficacy of a drug that had to be established before a drug was released for clinical use. Danny Freedman chaired a committee of the FDA, established to review all the psychiatric drugs available for safety and efficacy and I was a member of that committee.

DH: How did you team up with Sy Fisher and E. H. Uhlenhuth?

KR: I attended some early meetings that Jonathan Cole organized while he was head of the Psychopharmacology Service Center and Sy Fisher who was working with him at the Center was there. I think we first met at one of my visits to the Center and when we started to talk we realized that we had similar interests. And, then, I think he introduced me to Uhli and, in fact, Uhli and I are still friends. Then, we worked together for several years. In our experience antidepressants were not really very helpful in outpatient depression, and some anti-anxiety drugs were not only helpful in anxiety disorders but also in some patients with depression. This led to another series of studies. With Covi and Lipman, we compared chlordiazepoxide, impramine and placebo in a population in which half the patients were depressed and half the patients were anxious. This was prior to 1980, so we still called the depression we treated neurotic depression. Then we compared impramine, trazodone, diazepam and placebo in anxious patients and found that after about six weeks, imipramine caught up with diazepam and by the end of the study was slightly better. And, as you would have probably expected, it worked on the somatic aspects of anxiety. These studies clearly showed that benzodiazepines had only anxiolytic and no antidepressant properties. In contrast antidepressants, imipramine in this case, had both anti-depressant and anxiolytic properties.

DH: That's interesting. Just let me bring you back all the way to 1957 or 1958, when you began your research. How much nervousness was there perceived to be in the community? Did you know about those huge pools of community nervousness?

KR: Well, I don't know whether there was really much concern about that. Then, in the middle 1960's, David Goldberg developed the General Health Questionnaire (GHQ,) in fact, he spent some time in Philadelphia and we worked together. It was about that time I developed research collaboration with physicians in family practice. With my sociologist we studied the use of medications in family practice and the presence of anxiety in their patients. The GHQ is not specific for anxiety or depression. But, the thinking was, if you get physicians to recognize their patients have psychiatric problems, you might be able to treat their disorders sooner. The sooner you can detect the disorder, the better you can treat it.

DH: You mentioned one of the first drugs you studied was Miltown (meprobamate.) When it was released in 1955, the media picked it up quickly.

KR: There was Milton Berle, the comic, on TV. But the media picked up other drugs as well, for example, Prozac (fluoxetine). And depressed people seem to depend on carrying their antidepressant as anxious people depend on carrying their Valium.

DH: You raised the issue about people becoming dependent on these drugs. When did that become an issue?

KR: In the late 1960s there were observations there might be an increase in symptoms when you stop taking meprobamate. But it was only in the late 1970s I did the first long term study with anxiolytics in which we treated patients with diazepam, some for 8 weeks, some for 14 weeks, and some for 22 weeks. It was about that time we recognized that about 50 percent needed long-term treatment and 50 percent did not, although some did need it occasionally.

DH: We've jumped to long-term treatment from discontinuation symptoms with benzodiazepines. Could we get back to how the benzodiazepines came on the scene? Could you take me back through Librium, how you got hold of it, how it looked to you and then move on to Valium?

KR: Librium must have come about 1961.

DH: Was it prior to diazepam?

KR: It was. I did work with it before it was released.

DH: When you used it did you think this really is something?

KR: Not really. I thought it was like meprobamate. In fact, when I first started, I wasn't excited about it. Might be we didn't use it in the right patients. I'm not sure. Then Valium was introduced and it seemed that meprobamate produced more problems, in terms of discontinuation, than the benzodiazepines; very swiftly meprobamate developed a bad name. In the mind of researchers, clinicians and patients, meprobamate was put

more and more into the barbiturate type of drugs. But this had never been properly studied. These drugs were really a revolution.

DH: You said Librium came along first and it was not such a big change.

KR: The revolution started with meprobamate, it was the first of the newer drugs. Before, we only had barbiturates. Then, suddenly, it was replaced by the benzodiazepines.

DH: What was the difference between meprobamate and the barbiturates, other than being safer in overdose?

KR: There were not many studies comparing meprobamate and barbiturates and at the time we were not concerned with discontinuation symptoms. Probably the benzodiazepines worked a little bit faster than meprobamate, probably one of the major reasons people focused on the benzodiazepines. And, then there was a dancer, a woman who developed side effects when treated with a benzodiazepine. This happened in the 1970s, before the attack on benzodiazepines in the United Kingdom.

DH: Who was that woman?

KR: I've forgotten her name. It was a woman, who should have never been treated with benzodiazepines to begin with. She made the headlines. There were hearings before Congress, but then the situation relaxed again Today, I work with family physicians and residents who refuse to prescribe benzodiazepines. They're using hydroxyzine, an antihistamine, instead in acute anxiety. I think that's wrong. Americans are puritans, and maybe people in Great Britain are puritans too. But, certainly, people in France are more relaxed and prescribe benzodiazepines much more. I don't see people dying more on French roads in car accidents because of that. There are now findings that show antidepressants don't work right away. It takes a while before they have an effect. And benzodiazepines don't have to be taken continuously. In our one-year follow up study we found that about 65 percent of the patients had a return of anxiety, but many have no anxiety for months. Why should these patients be continuously on medication? But not much research has been done in this area since we completed our studies. In these days people are not interested in studying how long one should treat patients. There's a lack of long-term studies.

DH: How much did the emergence of BuSpar play a part in running down the benzodiazepines?

KR: I'm not sure. We compared clorazepate with BuSpar and patients didn't improve as fast, so the benzodiazepine was somewhat better. I have been involved in looking at many other drugs recently, particularly 5-HT_{1A} receptor agonists. I think the problem with these drugs is their

side effects. If you're anxious, you don't want to be dizzy; nauseated, or to have lots of headaches.

DH: In the 1960's we thought nervous people in the community needed an anti-anti-anxiety medication, whereas in the 1990s we think they need an antidepressant. Do you agree?

KR: I don't know. To some extent, anxiety was viewed as a minor cousin of affective disorders. Anxiety was not considered as serious. People thought for many years it had no impact on society. Now we know differently. We realize the tremendous impact it has. In the study I mentioned before we compared clorazepate and BuSpar. Out of the 150 patients we had 18 diagnosed as panic disorder. Of these 18 patients, almost everyone on clorazepate improved whereas none of the patients on BuSpar did. Maybe panic disorder is just a more serious form of anxiety. My anxious patients are sweaty, have difficulties talking to people and fears of talking in front of groups. This is part of GAD.

DH: So, during the 1970s, panic disorder appears?

KR: The concept was introduced probably in the early 1960s, but was not taken seriously until Upjohn decided to look for an indication for their new drug, so they introduced it as a new diagnostic concept.

DH: Would you say it was Upjohn's influence that helped make people aware of panic disorder?

KR: They did a good job getting the national experts involved. Panic disorder is one type of anxiety disorder you can identify. It was treated before with MAO inhibitors. You can also treat it with imipramine. At the time we thought panic disorder is different from GAD because it responds to treatment with imipramine, but now it has been demonstrated that GAD also responds to imipramine. Today we use SSRIs for depression, panic and obsessive compulsive disorders, sociophobia, and, maybe, for GAD.

DH: What about cognitive therapy?

KR: In our department Aaron Beck and John Rush, who was a resident at the time, published that cognitive therapy was as good as or a little better than imipramine and amitriptyline. But they didn't say there were experts treating people with cognitive therapy and residents treating people with drugs. So, the drugs didn't come out as well as they should have. When we took a random sample of patients visiting family physicians and asked who wanted counseling or who wanted medication, 80 percent wanted medication.

DH: Could I ask you about that? Did you see a difference between males and females? My hunch is that asking women, they'd want to talk, and asking men, they'd want the pill? Have I got that wrong?

KR: I don't know whether we looked at that but we are seeing more women come to us with anxiety disorders. But even if people would prefer to be treated with behavioral approaches we don't have the necessary therapists. We are moving towards socialized medicine in the States; to break even a psychiatrist needs to see 4 patients in an hour. That's what practicing psychiatrists now have to do, with HMO's.

DH: But in that kind of climate, what we learned from your early work can't be used at all.

KR: Correct, and I'm concerned about that. At the same time, I don't think you have to treat patients for 50 minutes, 5 times a week. There should be a compromise.

DH: You pioneered the use of family practitioners in research. We have the same kind of networks in the UK. .

KR: Our network of family physicians differs from the GP networks in England.

DH: Why did you start working with family physicians in the early 1960s?

KR: Because, in one of our early studies, we found low socioeconomic and city hospital patients related differently to their medication than middle class patients. When we gave them barbiturates they loved it, whereas middle class patients would complain they cannot drive and cannot work, etc. So, we thought we should study these drugs in consumers treated in family practice. My problem was that since we developed this network, it tied me down to Penn. It took a long time to develop.

DH: You're fairly unique in that you've been 40 odd years in one place.

KR: Then I became interested in the assessment of psychiatric symptoms in non-psychiatric patients and extended my activities into obstetrics and gynecology. I did research in infertility and had a grant on how to treat it. We developed a whole program to prevent adolescent pregnancy. We compared psychiatric symptoms in patients who had an abortion with those who did not and those who never had a baby with those who had. I published our findings in this area of research in a book a few years ago.

DH: Let me take you through another line of the work. You served on various committees.

KR: The first committee I served on was on drug efficacy and safety. Then, I chaired an FDA committee that dealt with daytime and nighttime sedatives. I was an advisor to the FDA for a number of years.

DH: Can I ask you about the issue of drug dependence and especially of dependence on benzodiazepines?

KR: It is not the same kind of dependence as opiate dependence. It's much easier to come off benzodiazepines than opiates

DH: There were also people who became drug dependent on neuroleptics. When they were taken off the drug they had withdrawal symptoms.

KR: If I take someone off a medication, I taper the drug gradually. Now we have to do it with the SSRI's, as well. One of the reasons that good therapists never had this problem with meprobamate or diazepam was they took patients off gradually.

DH: You've raised the issue of people becoming dependent on the SSRI's.

KR: I'm saying when you're taking patients off a medication they have some kind of discontinuation symptoms. I didn't say people were dependent on these medications.

DH: What you are saying then is that some people on benzodiazepines have discontinuation syndromes, but they're not necessarily dependent on the drugs. And patients who've been on Prozac (fluoxetine) for 8 years have not become dependent on the drug.

KR: We also talk about psychological dependence. Some patients are taking 5 or 10 milligrams of Valium for 10 years and doing well on it. The drug is like a crutch for them. Why should I take it away? This may also be the case with Prozac. The patient believes it helps and taking the drug provides psychological support. I have no problems with that. The problem is the patient who increases the dose. A few years ago I was called about a 65-year old woman on 5 mg of Valium for some time. She had several illnesses and one of her doctors, when she was hospitalized, called me and said the patient is addicted to Valium. He took her off the Valium and put her on imipramine. A few weeks later I learned she was almost operated on for what turned out to be impaction. Taking imipramine caused more serious adverse effects than 5 milligrams of Valium.

DH: I hadn't realized things had got so extreme in the US. We were like that in the mid to late 1980s.

KR: I think it's ridiculous.

DH: When you go to Japan, they don't seem to have the same problems. They describe some withdrawal problems, but they seem to be less frequent and severe. Is it genetic? Is it cultural?

KR: I say both. It's probably a bit genetic. Also the doses in Japan are usually lower than we prescribe here.

DH: They haven't had the problems with benzodiazepines and they don't have SSRI's.

KR: Patients with major depression don't care about side effects as much and no one has told me SSRI's are better than imipramine or amitriptyline. But SSRIs are certainly much safer for outpatients and especially for those who have tried to kill themselves.

DH: The world has changed since you began your research. I'm sure the issues discussed at ACNP were completely different in those years compared to now.

KR: ACNP is almost 40 years old. I'm one of the charter members. When we started, neuroscience hardly existed and 95 percent of the presentations were clinical. We can do things now we couldn't even imagine when ACNP started.

DH: How has the ACNP changed? I understand it was a small group, much more informal, and had a lot more brainstorming sessions. Now you have become the establishment; you're not the rebels you once were.

KR: That's right, but some of the older members of ACNP miss lack of the clinical context in current meetings. We're becoming almost part of neuroscience. Our founders, including me, didn't think the ACNP should be a neuroscience organization. It was supposed to apply neuroscience to clinical problems.

DH: On that point, there's an awful lot of neuroscience at this meeting, but how much of it feeds back into clinical practice?

KR: I don't know.

DH: Not a huge amount, probably.

KR: I would say that attending ACNP meetings now you'll get nothing you can apply in your practice. This wasn't the case twenty years ago.

DH: Twenty years ago you're saying you'd come to these meetings and get something useful for clinical practice?

KR: You would get something you could apply when you went home. I also think we have much more representation of industry now. It's a change.

DH: Did Beecher come to these meetings?

KR: Oh, yes. He was a member. My research was very much influenced by him.

DH: What was he like?

KR: He was an interesting fellow. The story is he loved to go to the basement of the library at the Institute of Medicine and knew exactly where the best pornographic books were.

DH: Really?

KR: He was a funny guy, though.

DH: How does the future look to you? You said people are becoming interested again in some of the things you did in your research.

KR: People talk again about the placebo response, and realize some of findings in the 1960s have bearing on contemporary clinical studies. No important new drug has emerged in the anxiety area. We looked at many drugs over the years but couldn't find any that were particularly

interesting; they were just not very good. When we have a drug with the efficacy of BuSpar, it's hard to show.

DH: There were great hopes for BuSpar. Do you think it failed?

KR: Certainly it failed as an acute treatment. .

DH: Is it not the same kind of delay in onset as with antidepressants?

KR: I always described buspirone as a kind of antidepressant rather than an anxiolytic. In fact, we demonstrated it has antidepressant effects. We did a study in which we compared imipramine, buspirone and placebo and found imipramine better than buspirone and buspirone better than placebo. So I think it is at least as much, or maybe even more, an antidepressant than an anxiolytic. It also has the side effect profile of antidepressants.

DH: It's an interesting drug from that point of view and it is also interesting that industry went down the anxiolytic route. The SSRI's seem to be the same kind of drugs.

KR: There was as much proof of that for BuSpar. The big problem with buspirone in Germany was it fell completely flat on its face.

DH: We need to draw this to a close. Thank you very much.

KR: Thank you for asking me, David. I enjoyed it.

ALAN F. SCHATZBERG

Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December, 12, 2001

TB: This will be an interview with Dr. Alan Schatzberg* for the Archives of the American College of Neuropsychopharmacology. We are at the 40th anniversary of the College in Waikoloa, Hawaii. It is December 12, 2001. I am Thomas Ban. Let us start from the very beginning. Tell us where and when you were born, something about your early interests, education and professional training?

AS: I was born in Manhattan in New York City in October, 1944. My parents immigrated to the United States in January 1940, after the onset of the war in Europe. They came from Vienna. My father went to Vienna in 1914 from Galicia, and my mother went from there in 1922, to be a college student. She met my father and they got married. My father was a 1925 graduate of the University of Vienna Medical School. His two brothers were also graduates. My father was a dentist in Europe. Because of anti-Semitism many Jewish doctors became dentists. Dentistry in Vienna and in many European countries was a sub-specialty of medicine. When my father came to the States, he became a general practitioner, practicing in the Bronx. I have an older sister who was born in 1934, who is a psychiatrist in New York City. She trained at Columbia. So medicine is an important profession in the family.

TB: Were your grandparents also in medicine?

AS: No. My grandfather on my father's side managed a wheat mill and my grandfather on my mother's side was a successful businessman in Galicia, in the lumber and leather tanning business, the kind of occupations that European Jews participated in. They were upper middle-class folks who left after the onslaught in Vienna. I was born in the States, but my sister was born in Vienna. So I grew up in the Bronx, went to Bronx High School of Science and after three years to college than on to medical school at NYU. At that point, they had an uptown campus in the Bronx. After graduating, I did my internship in pediatrics and medicine. For residency I went to Mass Mental Health Center, the main Harvard Medical School psychiatric teaching program and was there from 1969 to 1972. At Mass Mental, I met Joe Schildkraut and that was important in terms of my career. From 1972 to 1974, I served in the US Air Force during the Vietnam War, stationed at the Pentagon helping the Air Force set up drug and alcohol abuse programs and also with programs in

* Alan F. Schatzberg was born in Manhattan, New York in 1944.

race relations. They were very forward thinking, trying to deal with racial integration in the US Air Force. After two year, in 1974, I went back to Harvard and was recruited by Shervert Frazier at McLean Hospital to set up a depression research program with Joe Schildkraut, who was still at Mass Mental Health Center. He was the catecholamine hypothesis person. I was also scheduled to work with Harvey Schein, a virologist and psychoanalyst, who was the clinical director at Mass Mental Health Center and professor at Harvard, but who tragically passed away at a relatively early age before I arrived. Shortly after I got there, Jonathan Cole moved from Boston State to McLean. Jonathan and I became co-research partners, collaborative colleagues and friends. So I had these two very important people in American psychiatry as mentors; they got me interested in depression research, and so that's how it started.

TB: What was your first research project? Was it a project with Joe?

AS: My first publication was a single author paper; today these are rare, but it was on the trial and appeal of Wilhelm Reich, published in the Archives of General Psychiatry. Mass Mental was a very rich place intellectually and a fun place to be. In learning about psychoanalytic theory at the time, I came across some stuff about Wilhelm Reich and, having grown up in New York, I knew a little bit about what happened to him. It was a tragic story; he died in prison.

TB: Would you like to tell us more about your paper?

AS: I went to the US courthouse and got hold of transcripts of Reich's trial and appeal. This is particularly interesting because Reich was quite paranoid and fired his lawyer. His original lawyer was James D. St. Clair who represented Richard Nixon in Watergate. Reich represented himself and wrote his appeal that has become a rich source for seeing his paranoia. Danny Friedman liked the paper, and published it. Before I got into depression research, I also did some work in sexual behavior with Lee Burke at Mass Mental Health Center and in the psychological aspects of drug abuse, publishing papers with Ed Khantzian and John Mack, who were at Cambridge. When I got back from the Air Force, I started work with Joe and Jonathan on catecholamine turnover and responses to norepinephrine uptake inhibitor drugs. Joe was very interested in MHPG, and data which indicated that people with low catecholamine turnover seemed to be responsive to norepinephrine uptake inhibitors.

TB: Am I correct that you have continued that research and just a couple of years ago still published on MHPG and drug response.

AS: We have. We looked at catecholamines as differential predictors to desipramine and nortriptyline, tricyclic drugs we did a lot of work with,

and fluoxetine, an SSRI. We predicted that people with high average MHPG levels would be SSRI responsive but what we found was that the people with low MHPG levels were generally responsive to all those drugs. So that led to further confusion in the field. We also did a fair amount of research with Joe, looking at so-called "computer algorithms of catecholamines" and catecholamine metabolite excretion. We were developing D-type equations which looked pretty good at separating bipolar I depressives from unipolar nonendogenous depressives. We were one of the first groups to show a linear correlation between the excretion of urinary MHPG and urinary cortisol; that finding has been replicated several times, looking at plasma, CSF and whatever. A paper last year in PNAS showed that norepinephrine and CRH go together. So this high output state, described by us in 1983, has been replicated and that's nice. At the same time, because we were looking at MHPG as a predictor of response to antidepressants, we became very interested in lots of issues about depression and especially refractory depression. Why are some patients non-responsive to antidepressants or they don't tolerate the antidepressants? Sometimes they don't take enough, either because the physician doesn't prescribe it or because they can't tolerate it. So we became very interested in how to define treatment resistant depression. This is another place that you did a tremendous amount of work in 20 years ago, as did a number of people. We organized, in the mid-1970s, a symposium at the APA on treatment resistant depression in Atlanta. It was John Davis, myself, Sandy Glassman, Jon Cole and I forget who else. We were hoping we'd get 100 people to attend and when I walked into the room, there were 700 people there because this was a common clinical problem. So depression has always been our big interest and we've continued to do work in that area.

TB: Could you say something about your two "mentors," Joe Schildkraut and Jon Cole?

AS: Well they are diametrically opposite personalities. Joe is compulsive, careful, methodical, nitpicky, doing it in his own way, an incredibly good scientist but at the same time, what people don't realize about Joe, enormously creative. He has a tremendous vision and is a very interesting person. He is also one of the great experts in the world on Joan Miro and when the Guggenheim did a retrospective on Miro, about six or eight years ago, they had five citations, one of which was Joe Schildkraut's paper. And Joe also authored a book that is a compendium of presentations called *Homage to Miro*, published by Abrams. It's a terrific book based on a symposium he organized with Nancy Andreason at

the Miro Foundation. He has also written some wonderful papers about the New York Expressionists School including Jackson Pollack, Gorky and others; so he is a real renaissance man and a genius. Jonathan is a totally different person, lovable with an infectious personality, charming, witty, and generous to a fault, somebody who does not care about appearances. He has made tremendous contributions to psychopharmacology as one of the first President's of the ACNP and Director of the Psychopharmacology Service Center. I was fortunate to have both of them as mentors, even though each could drive you crazy in different ways.

TB: What was your first project with Jon?

AS: I think our first paper looked at tricyclic side effects. We did a paper on speech blockage, word finding problems that people on tricyclics have. We described a series of cases and what to do about them. We published an interesting paper in Archives on preventing seizures due to maprotiline, which is a drug you were heavily involved in developing. We had about 14 seizures at McLean, so we were able to document that the seizure was due to dose escalation. We also showed what the plasma level threshold was for seizures and worked with Ciba-Geigy to change the package insert to recommend a 75 mg initiation dose for two or three weeks before increasing to the maximum dose, with a roll-back after six weeks. We did a paper on trazodone in refractory depression and a study on thioridazine in borderline personality. Jon was very helpful to our group when we got interested in the question of psychotic or delusional depression and we came out with our first hypothesis paper in 1985; he was one of the authors with Tony Rothschild, Phil Langley and Ted Bird, director of the brain bank at McLean. Jon and I, in 1975, started an affective disease program that may have been the first specialty mood disorders program. We remained co-directors until I left McLean in the late 1980's and our first resident was Bruce Cohen, now the general director at McLean and a very well-known geneticist in bipolar disorder. Jon was an incredible mentor to young people and he, more than I, helped to train a number of terrific people, Sue McElroy, Paul Keck, Steve Hyman, Bruce Cohen and Trey Sutherland,who was at the NIMH. Tony Rothschild came through the mood disorders program, and Jon's enthusiasm and help was a boon to these folks. We taught them psychopharmacology.

TB: You wrote a book with Jon.

AS: In 1986 we came out with our *Manual of Clinical Psychopharmacology*. The American Psychiatric Press asked if we would do a book on psychopharmacology. Jon decided we would if we could make it a

non-exhaustive reference because there were other books, like the Kline-Davis book, which summarized the evidence base but weren't so useful for practitioners. There were things we agreed with in the literature and other things that didn't make much sense, so we wrote a book where we talked about how we practice and which gave people tips. We are now completing the 4th edition of that book. The first three editions sold about 70,000 copies, so it has been a tremendous success in the field, and Jon and I remain co-authors. We've added a third co-author because of our schedules; a young faculty person at Stanford, Charles DeBattista. It has been great fun and it also has some humor in it. You can actually read the book; it is spiral bound and it's done very well.

TB: Was it translated into any other language?

AS: Into Portuguese for Brazil and maybe into Italian. A lot of practitioners use the book around the world.

TB: Could you say something about the drugs you studied in your affective disorder program?

AS: We studied them all, including trazodone, maprotiline, bupropion and fluoxetine. Jon was very involved with bupropion development.

TB: In the 1980s, when the shift to SSRI's came, were you very involved with their clinical development?

AS: We were. Jonathan did one of the trials of fluoxetine in the mid-1980s and it was released in January of 1988.

TB: So, the affective disorder program at McLean Hospital was involved in clinical studies with new drugs?

AS: McLean Hospital was a very exciting place with a wonderful faculty. A person who was very important in my life was Shervert Frazier, Chief of Psychiatry. He was a visionary person who brought in many talented people. There was Evelyn Stone, a consulting editor for American Psychiatric Press, who was interested in education. In 1977, at the American Psychiatric Association meeting in Toronto, Shervert, Evelyn, Jonathan and I organized a McLean symposium on benzodiazepines that included Don Klein and Dave Greenblatt. We had Wyeth as sponsor and it was a great success. There were 800 people in the room on a Sunday afternoon before the meeting started. This was such a success so every year, from 1977 on, McLean Hospital would have a symposium at the annual APA meetings.

TB: Didn't you write a paper on the overuse of benzos in depression around that time?

AS: We did. I was involved with Jonathan with benzos in two or three different areas. He obviously had a very strong interest in them as anxiolytics

but he also had a very strong interest in benzos because of their abuse liability. So he had developed a model for studying that. At the time I had an interest in alprazolam as a potential antidepressant, so we did do some studies with alprazolam to test that. So I became interested in the whole question of overuse of benzodiazepines in depression and the question of diagnosis; we published a paper in 1978 in the Archives about that.

TB: McLean Hospital organized a symposium annually at the APA meeting?

AS: From 1983 to 1986. While Sherv Frazier was Director of the NIMH, I became the acting interim Psychiatrist in Chief at McLean. Since we had done studies with fluoxetine we thought, in 1985, we should do an APA symposium on serotonin because fluoxetine and several other drugs were being developed that had effects on serotonin re-uptake. We organized a symposium for Sunday morning at the APA and fifteen hundred people showed up. The place was packed. The Lilly people in the back just couldn't believe it! Their projection for fluoxetine sales for a year or two was only about $100 million. By the time the drug went off patent, in the US alone, sales were about $2.5 billion. We had our symposium two or three years before fluoxetine came out on the US market. So we worked with some very successful drugs like fluoxetine, but we also worked with other drugs that didn't make it. Oxaprotiline was one that didn't make it and adinazolam was another. A lot of the drugs didn't make it for toxicity or other reasons.

TB: We keep on referring to McLean Hospital. Could you tell us something about its history?

AS: McLean Hospital was founded in 1811 or 1812, as part of Mass General. Originally, it was in Charlestown, Mass where the Bunker Hill monument is and across the river from downtown Boston. McLean moved, in the late 1800's, to Belmont, Massachusetts to a campus of a couple of hundred acres and multiple buildings where people with disorders like Alzheimer's or dementia praecox could be hospitalized. There was no insurance in those days, so they were from families with wealth and a number of very famous people were hospitalized there. Alfred Stanton was Psychiatrist in Chief in the early 1970s and had an interest in the psychotherapy of schizophrenia. He was a well-known psychoanalyst in Washington, DC before being recruited. In 1972 Sherv Frazier went there and started to recruit people. He recruited John Gunderson to work with Al Stanton; Jonathan Cole and myself in depression work as well as Seymour Kety, Ross Baldessarini and Joe Lipinsky from Mass General. He set up a bipolar and schizophrenia program. Then, eventually he recruited Phil Holtzman, Steve Matthysse; Jack Mendelson,

Nancy Mello, Roger Meyer and Steve Mirin for drug abuse with Ed Shapiro for family therapy. He recruited outstanding people and built the Mailman Research Center, an unbelievably vibrant place. The transformation of McLean began in 1972; I went there in 1974; Jon joined at the end of 1974; Kety came in 1975. And as I told you, when he went to NIMH I took over for two years. After he came back I stayed, and from 1986 to 1988 I was running a large service and was an Associate Professor at Harvard Medical School. Then, in 1988, Miles Shore, the Director of the Massachusetts Mental Health Center, recruited me to become the Clinical Director and a full Professor at Harvard. I moved in 1988 but kept my research group at McLean. I also had my private practice there. The Massachusetts Mental Health Center was a very different place. It was a state hospital basically; Joe Schildkraut was still there with his lab but was totally dependent on my clinical operation to produce the subjects for our research at McLean. So Joe wasn't doing much research at Mass Mental itself. Mass Mental got some money from the state, and when I moved over, I began to transform it into a kind of "intramural" research operation. Alan Greene had been an extremely productive researcher with atypical antipsychotics and Carl Salzman was doing work in geriatrics. So we were able to start doing research at Mass Mental Health Center while I was there from 1988 to 1991. After I left, Miles retired as superintendent and went to the Harvard School of Public Administration. But research in schizophrenia continued with Alan Green, Bob McCarley and others.

TB: When did you move to the West coast?

AS: In 1989 Stanford started recruiting me as Chair of Psychiatry but there was a complicated arrangement and so I eventually moved in August of 1991. I've been at Stanford as Norris Professor and Chairman of the Department since 1991, just over 10 years. For a while I continued to do some research at McLean, although that petered out.

TB: What do you consider your most important contribution to the field?

AS: I think our current work on glucocorticoid dysregulation in psychotic depression is going to be extremely important. This work started at McLean with an observation that patients who were depressed and delusional, about 15 to 20 percent of depressed patients, have enormously up-regulated hypothalamic-pituitary-adrenal axis activity with excessive production of glucocorticoids. We've been able to show they also have a very clear cognitive deficit which involves the prefrontal cortex, probably the hippocampus and temporal lobe regions. We complemented these clinical findings with research in primates in which we showed these regions are rich in low affinity glucocorticoid

receptors, the so-called GR receptor, and that administering glucocorticoids to man or to primates produces cognitive problems very similar to psychotic depression. I recently reported with Joe Belanoff, (and we have another paper coming out based on a larger study), that mifepristone, which originated as RU-486, the French abortion pill, can rapidly improve psychosis in depression. We see 30 to 40 percent improvements in the BPRS scores in less than a week. The reason mifepristone works is that, while in low doses it is a progesterone antagonist, at high doses it is a potent antagonist for the low affinity glucocorticoid receptor in the frontal cortex and hippocampus, which is activated in periods of extreme stress. Since mifeprestone has very little effect on Type 1 mineralocorticoid receptors which mediate circadian rhythm and some other functions of glucocorticoid activity, we can block the bad part of cortisol release rapidly by using the antagonist. We're very excited about this work and are currently in Phase III with the studies. The development is by a company called Corcept I have been involved with. Organon is looking at a compound which has similar effects. This could be a very intriguing breakthrough for the field.

TB: And this project stated with a clinical observation?

AS: Totally, from two clinical observations. One was that when we looked at 100 patients at McLean Hospital we saw some patients with enormously elevated post-dexamethasone cortisol levels who were all delusional and psychotic. We then did studies looking at dexamethasone effect on dopamine metabolism by measuring homovanillic acid (HVA,) and got some signals from there. We developed the idea this was not an epiphenomenon, the result of depression, but might be the cause of some symptoms. Not necessarily the cause of the depression but of cognitive problems in psychosis. So it started from those observations. A lot of our work is funded by the NIMH. I'm particularly proud of this body of work we've been working on for almost 20 years.

TB: So, you already have some publications on this project?

AS: Jon Cole is on the paper we published in Joe Schildkraut's journal, the Journal of Psychiatric Research that Seymour Kety founded.

TB: You mentioned that besides mifepristone there is another compound in development with a similar action for the same population.

AS: Organon has a compound, but they are not studying it in psychotic depression because of certain intellectual property issues Stanford has.

TB: I see.

AS: I'm not totally convinced it's going to be a widely used drug because most depressed patients don't have increased glucocorticoid activity but it will possibly be for the most severe, psychotic patients. We're

particularly excited because this may be the first time we have a drug that starts with a clinical observation and ends up with a specific treatment. Tony Rothschild was supposed to present some of our recent findings today but I will be presenting because he couldn't attend. Tony did an amazing study in which he took psychotic and non-psychotic depressed patients and controls and showed a nice relationship between cortisol activity and cognitive dysfunction. So this work has been totally exciting for us.

TB: It seems the population you are working with is biologically more homogeneous than other depressive populations in psychopharmacology.

AS: Yes. We have already contributed to an understanding of the biology of this population but if we can come up with a treatment that would be a terrific breakthrough.

TB: So, you consider your number one contribution to be glucocorticoid dysregulation in psychotic depression with cognitive deficit and its possible treatment. Any other exciting work you are doing?

AS: We are doing research in a squirrel monkey colony that Seymour Levine, a very well-known psychobiologist, retired from Stanford, put through a variety of early maternal-infant stressors. We reared six mothers and infants from this colony without the father. Then we looked at their responsiveness to stress at the point of weaning, at age three and in early adulthood, as well as their hippocampus size. We found that hippocampus size was not determined by early stress but by who the father was. So it's probably not so much that depression makes your hippocampus smaller but that there are people with smaller hippocampus sizes prone to develop PTSD or depression. That's going to be an important paper in this month's Archives of General Psychiatry. It's going to be important, although controversial

TB: Any other exciting projects?

AS: The third thing is recent work presented in a poster here. It is a study with mirtazapine versus paroxetine, done with a young faculty member of the department, Greer Murphy, a terrific geneticist, in which we've been able to show that a SNP of 5-HT_2 could predict dropouts on paroxetine. So we may have, for the first time, laboratory tests to predict which patients can tolerate SSRI's.

TB: Have you followed up your research on norepinephrine in depression?

AS: I did some research with Joe Schildkraut in that area. In the last few years with the advent of drugs like venlafaxine, mirtazapin and reboxetine there is greater awareness of the role of nepinephrine in depression. The SSRI's as a group, they are great drugs for the mildly to moderately anxious and depressed person, but they may be lacking

effectiveness in more severely depressed or retarded patients. When I started what we called depression was different from what we call depression now. Nowadays, if you have four symptoms on the DSM you make the diagnosis "major depression". We wouldn't have considered those people depressed in the old days. Back then patients we called depressed were very impaired and many were near delusional or delusional. It's in that group I think norepinephrine plays a key role.

TB: Do you think there is a differential response for the more severe patients to norepinephrine re-uptake inhibitors?

AS: It's an interesting question. When you do meta-analysis, it's very hard to show the SSRIs are less effective. You talk, particularly to the Europeans, and they'll tell you that SSRIs are less effective in the more severely ill, and they have data to support that. They don't even use SSRIs in severe depression. If you look at data on reboxetine and some of the Italian data on reboxetine against fluoxetine, if you look at data on venlafaxine against fluoxetine, then norepinephrine re-uptake inhibitor drugs or mixed uptake blockers, do better in severe depression. If you look at FDA submissions about half of inpatient studies have shown that venlafaxine and reboxetine would be better than the SSRI and about half not. And I know of almost no studies that show an SSRI more effective in those patients. They are better tolerated but I think that's where people miss the point. For the vast majority of patients Sherv Frazier used to call the "walking wounded", the SSRI's are good drugs. They are anxiolytic. They help despondent mood. They help mild to moderate depression. But for the more severely ill depression, the tricyclics, which were tougher to tolerate, were probably more effective.

TB: You had done some research on the side effects of tricyclics. Now what about side effects with SSRI's?

AS: They are much better tolerated and most of the side effects are gastrointestinal. About a year or year and a half ago I participated in a study in which we compared sertraline and desipramine and we found that men tended to be more responsive to desipramine and women had lower drop-out and better results, with SSRI's. So there may be not just severity but also gender and estrogen levels relevant to effectiveness of SSRIs. There is now a European study on fluoxetine that also showed women do better with SSRI's. When, in 1988, fluoxetine came on the horizon, the reason it did so well was because there were a lot of women who couldn't tolerate or didn't respond to tricyclics. For men, the SSRI's are a mixed blessing; delayed ejaculation in men is more problematic and men may respond better in terms of mood to the

tricyclics. There are some data, particularly on sertraline, that men are less responsive to sertraline than to a tricyclic.

TG: Did you do any research in bipolar patients?

AS: A little bit. We did less than we would have liked because McLean became specialized and the Kety, Lipinski, Ross Baldessarini group had done the bipolar research. When we did bipolar research, it was around bipolar depression, looking at catecholamines. We did do some work with lithium augmentation, lithium side effects and things like that, but were less involved in bipolar research. Even to this day at Stanford, I don't do much bipolar research because I have a very good person, Terry Ketter, who heads up the Bipolar Program for us and does the bipolar work. He has a couple of posters here as well.

TB: About the same time the SSRI's appeared in the 1980s, atypical antipsychotics were introduced. Would you like to comment on them?

AS: Atypical antipsychotics are very interesting drugs and I was fortunate at the Mass Mental Health Center in 1988, to do some work with clozapine in collaboration with Alan Green and Jon Cole that led to the publication of a couple of papers. In one paper we reported a tremendous increase in circulating plasma norepinephrine in response to clozapine. It was probably because of it's α_2 antagonism. We also did a study in the most severely ill, refractory bipolar patients, who were non-responsive to traditional neuroleptics, lithium, Tegretol (carbamazepine) or valproate and treated them with clozapine. We had about two-thirds of these patients dramatically better with clozapine. It took us about two-years to publish our results in the *American Journal of Psychiatry*. But it was one of the first reports on the use of an atypical antipsychotic in severely refractory mania. Now you have olanzapine approved for these patients. I think atypical antipsychotics are probably quite effective for acute mania. But the problem with atypical antipsychotics is they produce side effects that are problematic, mainly weight gain. Whether they cause Type 2 diabetes is in debate, but they certainly cause weight gain and that is problematic for maintenance treatment. But for acute treatment and people who do not gain weight, the atypical antipsychotics are very good agents. I forgot about those studies. Thanks for reminding me.

TB: Are you still seeing patients?

AS: I still see patients.

TB: So you are involved in basic and clinical research, teaching, clinical practice and administration?

AS: Yes, and I run the department and the department runs me. I see patients Wednesday afternoon, when I'm in town and 400 or 500 patients I follow in consultation together with someone else.

TB: So you follow many patients?

AS: All with mood disorders. I teach residents, medical students and run the department. I have been fortunate to keep up a very active research group with a number of interesting studies in animals and in man. We're doing a lot of functional imaging, particularly with glucocorticoid antagonists. I've been fortunate to be more productive, in terms of my research, at Stanford than at Harvard and part of it has to do with the structure of the places. Stanford is very research oriented. Some of the Harvard programs are hospital-based, where Stanford is much more university-based and it's a lot easier to do research. I have people on our faculty and in our department to collaborate with, geneticists and people who do functional imaging. We're heavy users of the General Clinical Research Unit, where we do our HPA axis studies. I've been fortunate, as a Chair, to be able to continue my own research because I have such good people around me. The job of the Chair has become more and more arduous with managed care, family practices and hospitals stuff. What's been a godsend in my career is I don't think I've peaked in my research; a lot of people peak in their 40's. I'm 57 and I'm doing the most exciting work I've ever done and the most independent work. At Stanford, I have a large clinic but a small hospital service, so I can free myself up to do my own investigations.

TB: It seems that all through your professional career you have been working closely with patients.

AS: Yes, very closely. That's where you learn.

TB: Your activities are very well documented in your publications. You started to publish in the early 1970s and you keep on publishing. We have already talked about some of your publications, could you review those you consider most important?

AS: The papers on delusional depression and DST abnormalities published in 1983 in the American Journal of Psychiatry, our papers on cognitive deficits published in 2000 also in the American Journal, a paper on ACTH published in 2000 in the Archives, a paper on psychotic depression published in 2001 in the American Journal, and our mifepristone paper, published in October. Some of the other papers are just as important, as for example the paper on glucocorticoids versus dopamine in the Journal of Neuropsychopharmacology, the papers with Joe Schildkraut on MHPG, the papers on benzodiazepines and depression, some of our side effect papers, the paper on withdrawal hypomania, our pharmacogenetic papers and our papers on imaging in the monkey the hippocampus size. We tend to be a bit contrarian, although to some

extent our findings go along with what Strömgren referred to as reactive psychosis.

TB: Are you referring to Strömgren's postulation that reactive psychoses are based on genetic predisposition?

AS: Yes, that for reactive psychosis you need a predisposition. .

TB: Would you like to say something about your books? You already mentioned the *Manual of Clinical Psychopharmacology* is going into its fourth edition.

AS: In 1988, with Charlie Nemeroff, we published one of the first comprehensive *Textbooks of Psychopharmacology* that engulfs basic to clinical aspects of the field. We are now preparing the third edition of that text. We also did a primer of psychopharmacology that's in its first edition for the American Psychiatric Press. The textbook, *Essentials of Clinical Psychopharmacology* is coming out in paperback. Charlie and I have been very, very pleased about it. I think it's a terrific book. It did not have the sales of the Manual. It's a much bigger book.

TB: Didn't you say that the Manual sold about 70,000 copies?

AS: Yes, 67,000. I think the first edition of the textbook did about 11,000. That is very good for a textbook.

TB: It's very, very good.

AS: The second edition sold 7 or 8,000 copies. Anything over 5,000 is a huge success. We've been very, very fortunate. The books are good. It has been fun working with Charlie. He's a very good friend.

TB: You have been awarded and received honors for your work. Would you like to mention a few?

AS: The awards I'm most proud of are the Best Teacher Awards I got from the Stanford residents right after I got there, the Klerman Lifetime Research Award, the Klerman Award from Cornell Medical College, the Strecker Award from the University of Pennsylvania, the Mood Disorders Research Award from the American College of Psychiatrists, and the award from the Northern California Psychiatric Society for Outstanding Achievement. In the military I also got a Meritorious Service Medal. I've been blessed with this recognition and I am highly appreciative.

TB: You mentioned at the very beginning that you were in the Air Force?

AS: That's where I got that medal. They gave us the medal because they had to put up with us for a couple of years in those days. I was not exactly your typical US Air Force Major.

TB: When did you get involved with the American College of Neuropsychopharmacology?

AS: It was in the early 1980's I became a member; I've been coming to meetings for 20 years and it's the highlight of my academic year. The

College is an incredible place. It truly is a College. We've witnessed transformation over time. We've been able to grow, and it's been just a wonderful, wonderful experience.

TB: You were president of the College.

AS: I was President in 2000, and after the business meeting in a couple of hours, I will be the immediate Past President and Chuck O'Brien will be President. I was on the council for three years and took a year off before becoming president elect. Seven out of the last eight years, I've been very involved with running of the organization. It's a unique place. It is a place of tremendous friendship, tremendous collegiality. You see your friends, and see them working on scientific issues important to the field. The College has been enormously successful. The Nobel Laureates last year are important additions to Julie Axelrod. It's an organization that has meant a lot to me in my professional life. I've been on the program many times, although not every year; we usually present every two or three years. And we usually do a panel every couple of years. This year we're on two or three panels because I organized one on substance P and we have a panel on delusional depression this afternoon. We also have a few posters. It's a wonderful place to see people and the one meeting I look forward to. I go to a lot of meetings every year, but this is the one that really means something to me.

TB: Is there any other organization you have been involved with?

AS: I belong to the American Psychiatric Association, the American College of Psychiatrists, and the International Society of Psychoneuroendocrinology. I serve as their Secretary General. But, the International Society of Psychoendocrinology is a much smaller Society. It's very, very specialized. It certainly fits an area of my interests, but I have other interests as well. Still, there's nothing like ACNP. It's small enough to have fabulous meetings but large enough to include people of many different disciplines. One of the things Steve Paul, when he was President, started was looking at the holes in the College and trying to fill them in. We've been trying that actively this year, adding some child psychiatry researchers and others in research methodology and statistics. We need to find and add people in certain areas, to keep ahead of the cutting edge and I think we'll do it. It's a College that you were involved in earlier with Jon Cole, Frank Ayd, Heinz Lehman and others, in founding the organization. We owe all of you guys a tremendous debt of gratitude for having the vision to come up with it. Since 1961, science has changed, but the quality of the College hasn't. The quality always was superb and continues to be.

TB: Is there anything else you would like to add or comment on?

AS: Psychopharmacology has been a godsend when I think of patients I saw when I started in psychiatry. It was a big switch from imipramine to amitryptiline. Then we got into MAO inhibitors, which were great drugs, effective for lots of patients, but dangerous as hell. Now that we've got so many tools we're starting to understand the brain. But we have some real holes, for example the nomenclature we use, the classification we have. The change there will come through genetics and other techniques rather than through descriptive classifications. We mentioned that the diagnosis of major depression is too broad. We have a lot of people who meet criteria but are not really depressed, and that's something we're going to have to solve. The DSM has been helpful in providing a cross-practitioner language people could agree on, so it's reliable but it's not clear it's valid. To make that next move hopefully clinical biology will come up with innovative treatment strategies. We hope our work in psychotic and delusional depression is in that genre. It seems to me it is but it depends whether we can convert it to an effective treatment. That's the kind of thing we need to do so we can then have a better and more effective psychopharmacology. So that's the message I would like to leave in 2001.

TB: So, you're concerned about the nomenclature.

AS: It needs to be hooked up with genetics. We need a functional nomenclature that goes with genetics to develop new drugs. At the same time, even though I'm a psychopharmacologist, I believe in psychotherapy and the combination of therapies for most patients. Most patients need some sort of combination treatment and that needs to be taught. I'm concerned that some departments are moving away from it. You can debate whether we should be teaching more dynamics.

TB: Do you think we need to teach psychotherapy?

AS: I've been involved with Marty Keller in some very elegant studies on chronic depression. We published some papers looking at nefazodone in combination with a cognitive behavior therapy called CBASP, and are now going to do another multi-center chronic depression study, hopefully, funded by the NIMH. So I still believe in psychotherapy and I think it's important. I also think we need to study the biology of it. As we do more clinical biology, we need a little more gender-based sophistication. Our studies in chronic depression suggest gender plays an important role in drug response in premenopausal women. We need to understand that.

TB: You are involved in psychotherapy research as well?

AS: We still do psychotherapy and psychotherapy research in depression.

TB: What other interests do you have outside of psychiatry and psychopharmacology?

AS: I'm an avid reader but I read practically no fiction. I love books about history. I love reading about sports, adventure, mountaineering, and things like that. We travel a great deal, not only for business but for pleasure. We like the fine arts. I like the theater, and I'm a big sports nut. In the last few years I started to play golf, which is my nemesis although I enjoy it. And I like coming to Waikoloa because I get to play golf sometimes during the meeting, although when you're on the council it's a little tougher. Those are my hobbies and they keep me busy.

TB: Do you have a family?

AS: I have a wife, who I met at Mass Mental Health Center and who was a psychiatric nurse and became a psychiatric social worker. I have two daughters, one who is in law school and one who just graduated. Neither of them is married.

TB: Is there anything else you would like to add?

AS: No. Doing these interviews is an important thing Tom; we appreciate your dedication to the College and are indebted to you for developing this archival material.

TB: On this note, we conclude this interview with Alan Schatzberg. Thank you very much, Alan. .

AS: Tom, thank you.

NINA R. SCHOOLER

Interviewed by Thomas A. Ban
Waikoloa, Hawaii, December 11, 2001

TB: We are at the Annual Meeting of the American College of Neuropsychopharmacology in Hawaii. It is December 11, 2001, and I will be interviewing Dr. Nina Schooler* for the archives of the American College of Neuropsychopharmacology. I am Thomas Ban. So, let's start from the beginning. Could you tell us where and when were you born, about your early interests, and how you got into neuropsychopharmacology.

NS: It's a pleasure to be here and interviewed for the Archives. I was born in New York City in 1934, and was educated in New York City public schools, with the exception of a few years when I lived in Miami Beach, Florida. I graduated from the Julia Richmond Country School, which was not in the county, but located on the east side in Manhattan and then went to CCNY, the College of the City of New York. I was fortunate to be in the first class to which women were admitted to regular college other than to the college of education or the business school. I graduated from CCNY with a BSS degree, Bachelor of Social Science, in 1955, and went to work at a company called The Psychological Corporation, working in market research and coordinating the researchers who collected data for The Corporation. And, as I look back on my career, that's what I've been doing ever since; coordinating the collection of data. I entered Columbia University in 1956 to get a PhD in Anthropology. My undergraduate major had been Sociology it appeared to be a bad mix between marriage and Anthropology, which required travel to far away places. So I switched to an interdisciplinary program, Social Psychology, and completed my course work in a very expeditious fashion. Then, in the 1950's, my husband obtained his PhD and we moved to Bethesda, Maryland, where he had accepted a position in the intramural program of the NIMH. I became a stay at home wife, working on a doctoral dissertation. At the same time, I had a baby and maintained contact with my doctoral advisor at Columbia, Richard Christie, a very well known Social Psychologist, who was supportive, but, not particularly helpful, in what topic to choose for a dissertation. At that time, when my son was about two years old, I was told about a position at The Psychopharmacology Service Center of the NIMH. I was directed to call Solomon Goldberg, and the rest is history. That was

* Nina Schooler was born in New York, New York in 1934.

the most useful phone call I every made. Sol hired me as a research assistant, part-time. I was only willing to work part-time, because I had a small child turning three and starting nursery school. My view was that I would work when he was in school and when he wasn't I would be home with him.

TB: So, you started as a part-time research assistant?

NS: Sol later told me he had wanted a full time assistant and somebody who had a PhD. He turned out to be the most wonderful boss, collaborator and mentor.

The PSC was headed by Jonathan Cole, who was the most creative leader of a new field anyone could have imagined. This would have been 1962-63. The Service Center was new and Jonathan assembled a remarkable number of investigators in pre-clinical and clinical psychopharmacology, although nobody had a name in the field at that point. The NIMH then was a looser organization than it came to be later and Jonathan's creative juices were allowed to flow. He was able to do all sorts of wonderful and inventive things, in terms of distributing money to the field, mechanisms for providing support to do studies and so forth. When I arrived at the NIMH-PSC, the first collaborative study had just begun. This was a nine-hospital study, comparing three phenothiazines to placebo. Jonathan Cole and Gerry Klerman, who had been at the PSC for a couple of years, designed the study, Sol Goldberg co-ordinated it and I was his assistant. My background was in Social Psychology so I didn't know anything about psychopharmacology. I knew a little bit about methodology, not clinical trials, but experimental methodology. I understood the principles of randomization and a few other things, but not anywhere near as much as I learned over the next several years. Yet, because the field was so new and things were so open, I had lots of opportunity to do literally as much as I wanted. If I stumbled, someone would help, so it was a wonderful, wonderful opportunity. I can't stress enough the richness of the environment at the PSC and outside. But, not having my degree, I was pretty well invisible person in the organization. While I was allowed to do what I could within the organization, beyond it I was invisible. There was a lot of support for me to develop a doctoral topic related to what I was doing and enable me to obtain my degree. The system at NIMH allowed me time to write when I needed to write, to develop a data collection plan and to collect the data. At the same time, a wonderfully supportive faculty person at Columbia, while recognizing this was not an area of his expertise, was prepared to sponsor my dissertation.

TB: What was your dissertation on?

NS: The topic I chose was one which had nothing to do with psychopharmacology; it involved schizophrenia, the patient population of the first NIMH collaborative study, which has remained an area of interest from 1963 to this date. In some ways, that was happenstance. That was where I happened to fall, but in many ways it was an extraordinarily lucky opportunity, because schizophrenia was a fascinating disorder and remains so for me, today. My dissertation dealt with language in schizophrenia; I looked at grammatical linguistic distinctions and compared performance on a test I devised with schizophrenia patients and normal controls, matched for education. It's one of the embarrassments of my career, that the results have never been published anywhere, except in dissertation abstracts. I suppose that's because of the career direction I took. I have never thrown away the data and they probably still have relevance to the field of language and thought disturbance in schizophrenia. Maybe I'll get back to them one day. I obtained my PhD in 1969, when I was thirty-five, several years after my bachelor's degree. Here I want to digress for a moment to comment about the status of women in the field, at the time.

TB: Please do.

NS: In some ways, the status of women was easier in the 1960s and 1970s than it is today. Perhaps I can explain that by saying it was a time of low expectations. There's a line, I think, by George Bernard Shaw. When asked about women preaching his comment was, "It's like a dog walking on hind legs. You admire the fact that it does it and don't comment on the quality". And, in a sense, that the situation for women. For example, if you look at my CV, you can see a gap between 1955 and 1969, from my bachelor's degree to a PhD. In the case of a man, the question would be what happened during that period? Why didn't he get his degree more promptly? Is there something wrong with him? For a woman no one would bother to ask those questions. One year of the delay, between 1968 and 1969, could be attributed to the fact that my dissertation was locked up at Columbia University in the mathematics building, because of the 1968 student riots, so my sponsor was unable to review it.

When, finally I received the degree in 1969 I was admitted to full status in the PRC. Rather than just working within the department I was eligible and allowed to interact with the wonderfully burgeoning field of clinical psychopharmacology on the outside. One of Jonathan Cole's innovations was to create an external committee that reviewed grants in clinical psychopharmacology. He had done this because when grants that tested whether there was a difference between two drugs

went before the standard study sections at NIH, they did very poorly. The PSC had been established with money that was supposed to fund these trials. So, Jonathan had a mandate and needed a mechanism to allow him to fulfill it. And this review committee was one of the major mechanisms he established to do that. Now I had a PhD and could be addressed as Doctor, I was acceptable and presentable as a member of the staff at study section meetings. So, I started to get to know colleagues in the field. So it was in, I believe, 1970, I had my first opportunity to go to an ACNP meeting, held in San Diego. Sol Goldberg, who was still a close colleague, working together, invited me to the meeting to participate in an ongoing study, called Prediction of Response in Schizophrenia. He and Jim Klett were responsible for it and the group met throughout the meeting and persisted from year to year.

TB: What did you present on?

NS: I don't remember although I believe it had to do with the use of what we called performance tests, which are now known as neuropsychological or cognitive measures in schizophrenia. They were data from a second, longer term, collaborative study Sol had been instrumental in designing and I was involved in the conduct of. What I remember about the meeting are two things. First, the plenary session was on the topic of cyclic AMP and I sat for an entire morning understanding only the connector words in the sentences. I had no knowledge of what the meaning of the nouns was and no understanding at all of what was going on. My feeling was that this was a place that was not for me. I then participated in a study group in a relatively small room. There weren't more than fifteen or twenty people in the room; some of them I knew, and they smiled and said "hello." The others also seemed friendly. Everyone was very absorbed in the discussion; it was very collegial. I left for home with the feeling that, overall, the organization was vastly beyond my comprehension and a sense I had been in an environment that was much bigger than I knew or understood. I have been part of the ACNP since that time and some of that feeling of awe, of being part of something much bigger than I know or understand, persists. It is as though, even as my own knowledge base grows, the field grows more rapidly than I do. I still have some of that feeling, but nevertheless go to the plenary sessions and sometimes they work but sometimes they don't. This year's plenary session, I'm leaping from 1971 to 2001, was a good one for me and I attribute it to the organization of the topic, which was on substance abuse, and the quality of the speakers.

TB: I see.

NS: Now, I suppose I should go back to 1971, where I had found what felt like a very valuable and important niche within the PRB at NIMH. And that was in the design and coordination of multi-center studies in schizophrenia, and here I'll ask whether it's appropriate to describe the sequence of studies I was involved with?

TB: Of course.

NS: There were a series of studies I worked on from 1971 to 1988, the year I left the NIMH. They were all on schizophrenia; they all addressed important questions, and they were all studies which were difficult to carry out, so people were not likely to do them on their own. I've already talked about the first study, the one designed by Jonathan and Gerry Klerman, well before I got there, in which three phenothiazines were compared to placebo in a short six week trial. The second study, which was designed by Jonathan and Sol Goldberg, looked at the long term effects of three phenothiazines with no placebo, given that the placebo control question had been answered. This was followed by a study that Sol and I did in collaboration with Sam Gershon. It dealt with prediction of response and was designed to compare differential clinical profiles of patients responsive to two different phenothiazines. Then we went on to do a study with Jerry Hogarty that started one of the other strong interests I've had, in long term treatment and the interaction of psychosocial and pharmacologic treatments in schizophrenia. This was a two year study in which we compared chlorpromazine to placebo and to a psychosocial treatment, called major role therapy, or no psychosocial treatment. After that, this would have been about mid 1970's, Sol retired from the NIMH, to move to the Medical College of Virginia, and Jerry Hogarty and I went on to do a study in which we looked at the interaction of fluphenazine, long acting and oral, with psychosocial treatment. In a parallel study, Jerry Levine, who had taken over directorship of the PSC-PRB, and I designed and carried out a collaborative study. I believe it was done in four sites, where we compared injectable fluphenazine to oral fluphenazine in a one year long study. This four center fluphenazine decanoate study and the one in collaboration with Hogarty were the first ones where I had principal responsibility for design, conduct and coordination. I'd been doing the coordination for a number of years and that was more facilitative, carrying out tasks, but these were studies where the questions came from my thinking about the nature of the illness, and what the important treatment questions were. These were wonderful, wonderful opportunities for me.

TB: Could you tell us something about the results?

NS: Absolutely. The original first collaborative study showed the dramatic effects of three phenothiazine medications compared to placebo in six weeks. This was certainly not the first study to show that. There were certainly studies in the field which showed similar findings. What was important about this study was that it was in hospitals where people said it didn't matter if you gave people drug or placebo; places like the Institute of Living or Paine Whitney Clinic, which had wonderful clinical programs. The idea at the time was it only mattered in State hospitals, and this study showed the effects were uniform across all hospitals. The finding we had out of the second study was we could not distinguish among the drugs, but there were increasing effects out to six months. That was a very valuable contribution because it suggested the drugs were not short term, but there were long term effects that made a real difference in the lives of patients. There were also collaborative studies done in the Branch I was not involved with, which were long term in very chronic inpatients, while the initial studies had been done in acute patients. The first study had been designed for first episode patients, but when it turned out to be difficult to accumulate first episode patients they changed the inclusion criteria to acutely symptomatic patients. The two year maintenance study that Sol and I did with Jerry Hogarty, represented for many years, and possibly still does, the best demonstration of long term medication effects in schizophrenia. When people are looking for an estimate of the placebo response rate in schizophrenia over the long term, what is often cited is the non-relapsed placebo response rate after two years in that study, which was about twenty percent. Essentially, what we found was that medication represents a platform against which psychosocial treatment can operate, because in the patient group that received placebo, the intensive psychosocial treatment turned out to be deleterious; that was a very important finding, but not one that was immediately recognized. In our studies of long acting fluphenazine decanoate and oral fluphenazine we were unable to find a difference between the two which represented a great disappointment to many people in the field because the findings meant that compliance didn't make a difference. It was contrary to what every good clinician knew, namely that patients who don't take medication, relapse. We should have known, with hindsight, that the kinds of patients who agree to participate in a clinical trial are likely to be more compliant than the rest, so the study was biased against finding a difference. What we did find that had a major impact on my understanding was that even when patients take their medication exactly as prescribed, they can relapse.

TB: Very much so.

NS: Let me talk about my other activities at NIMH, because this was the research part and, in many ways, very fulfilling, but not the only thing I loved about my job.

TB: Please do.

NS: One of the things I loved was the fact I had the opportunity to interact with a broad field of people in psychopharmacology beyond the members of ACNP because our group was involved in reviews and administration of grants that came from the outside. One of the things that has been the most fun is to see people I knew as young beginning investigators, mature, become my colleagues and go on to very illustrious careers; now one of them is my boss!

TB: Could you mention a few of these people?

NS: When we compared fluphenazine decanoate to oral fluphenazine, Allen Gellenberg, who's now the Chair at the University of Arizona, was finishing a residency and starting as a research psychiatrist. He has become a colleague and friend over the years. In a more recent study, a young psychiatrist, Peter Weiden, also a resident when we started the study is now ready for promotion to Professorship with tenure at Downstate in New York. Then, in the last study I did at the Institute, Treatment Strategies in Schizophrenia, I worked with Sam Keith, someone I met when he was a young Fellow joining NIMH.

TB: When did you leave NIMH?

NS: I left NIMH in 1988, in the middle of the study, not as a retiree but as a resignation. The reason was that I was ready to move out from a protected environment in which I had grown up. I wanted to see whether I could make it in the real world. The first question was that I needed a job so I put out a couple of sort of tentative feelers, to find out if there were any appropriate positions for me in the academic world, within an hour airplane radius from Washington, DC., where my husband was. You can get to a lot of places in an hour from Washington. Another reason I wanted to make this move was difficulty in relationships with people in the field when you're in the extramural program of NIMH. Most decisions are made by review committees, and there were enormous checks and balances on the power of any given individual. I often had the sense people didn't believe me when I told them that.

TB: Where did you move?

NS: I took a position at the University of Pittsburgh in David Kupfer's department, directing a Psychosis Research Program, where, as David explained to me, "Whatever it is you do will fit within the parameters of psychosis research". He couldn't give me the word,"schizophrenia",

because that was already taken! I moved to Pittsburgh and because of the wonderful collaboration with Sam Keith and a junior colleague and biostatistician, Joanne Severe, at NIMH I was able to continue as primary director of the treatment strategies in schizophrenia study. That was wonderful because it was a study I was devoted to; I'd like to think it was also wonderful for the study, because we did carry it successfully to completion.

TB: Cold you tell us about the findings in that study?

NS: We used fluphenazine decanoate because that was the only way to guarantee our dosage comparison would not be diluted by noncompliance. We found the rate of relapse was quite low with the moderate dose of fluphenazine decanoate, that there was an increase in relapse with the low dose, and with the group that only received "rescue medication" at signs of prodromal symptoms, the relapse rate was substantial. We couldn't distinguish re-hospitalization rates between moderate and low dose groups, but we saw an increased rate of re-hospitalization with the prodromal sign intervention group which only received medication if needed. What that means is that when a low dose is used in maintenance and raised when there is symptom exacerbation in outpatients, it's possible to avert re-hospitalization. But, if there's no medication, as in the group that received medication only as needed, even an adequate dose of medication given at the initial symptoms, is not enough. This was in the context of an elaborate treatment team approach with families, because in order to be in the study, patients had to have a family member available. This was why we were prepared to take the risk of an early intervention strategy, because we had both a treatment and a family team in place. The other point that was significant was that the length of treatment exposure, two years, was critical to demonstrating these effects. If our study had only been three months long, we could have seen none of the medication treatment effects. If it had been one year long, we would have said the moderate dose was better than either the low or early intervention strategy, but we could not have distinguished the low dose group from the early intervention group. So it was only by going out to the second year we could successfully discriminate the three medication conditions.

TB: Now, it is 1988 and you had moved to Pittsburgh.

NS: When I moved to Pittsburgh, a decision I made independently, both of my sons had made the same decision the year before. One was a beginning assistant professor in the Psychology Department at the University of Pittsburgh and the other was a beginning graduate student in Psychology at Carnegie Mellon University. While I had moved away

from home, I had gone to the same place my sons were, so I had a very strong support network in Pittsburgh. When I arrived in Pittsburgh I had two interests I knew about on arrival, and both were at opposite ends of the spectrum in schizophrenia. One was in first episode schizophrenia. Since the original NIMH collaborative study, I was strongly interested in the question of what happened in schizophrenia if one examined it from the beginning?

TB: And the second one?

NS: The second was in chronic and refractory schizophrenia. So, within a month of my arrival in early 1988, I went to visit Mayview State Hospital, about fifteen miles and twenty-seven and a half minutes from Western Psychiatric Institute and Clinic, where I was based. The reason I can tell you, with such precision, how many minutes it took was that I made that trip virtually every week over the next ten years. We were able to establish a research ward with the support of the State and the Institute, so this was a collaborative effort between the University and the State facility. I had wanted to call the unit the Center for Community Asylum Treatment, intending the little "a" meaning of asylum, a safe haven. Nobody would allow that title. Everyone thought it was a terrible idea that was going to get us into real trouble. So what we finally called it was the Special Studies Unit, which everybody agreed to. We were certainly "special" and they allowed the word "studies", and that's the name of the unit to this day. What we were able to do in that environment was very, very positive. This was 1988, about the time the study with clozapine had been completed by John Kane, Herb Meltzer and their colleagues. Since the Mayview Hospital had been one of the sites, there was enormous enthusiasm for new treatments. So, within six months of arriving, I was offered the opportunity to participate in the study of risperidone that Janssen was conducting and this was my first industry sponsored venture. I had the good fortune of being in a place at a time where I could become actively and enthusiastically involved in the research on atypical or second generation antipsychotics.

TB: Could you tell us about the study with risperidone?

NS: Four doses of risperidone, haloperidol, and placebo were compared and all doses, from six to sixteen, were better than placebo. Haloperidol was also better than placebo. Haloperidol turned out to be a side effect disaster, in terms of extrapyramidal signs. That was because the dose was twenty milligrams a day. At the investigators meetings I tried to recommend the dose of haloperidol be changed, because I thought it was too high. As I subsequently learned investigator opinions are not seriously considered by industry. They may be noted, but they're not

wildly encouraged. But what was useful from my perspective was I learned how to contribute more directly to later studies, one in particular. This was a first episode study, also with Janssen, for which I was the lead investigator and compared risperidone and haloperidol, using haloperidol in appropriate dosages.

TB: How was the dose determined for the first episode study?

NS: On an a priori basis. The study is just finishing data collection. It was a double blind study in which doses of the two drugs were determined in milligram equivalents. In this study the milligram equivalent of risperidone and haloperidol was one to one, and the target dose for both was four milligrams. The investigator was free to use as many or as few of the capsules as desired, although there was an initial titration schedule. The reason I was asked by Janssen to work with them on this project was because we had developed a very excellent and elegant program in First Episode studies at Pittsburgh. This was in the context of a Center for Neuroscience and Schizophrenia, funded by the NIMH, for which, first Ed Streicker and, subsequently, David Lewis, have been the directors. Because the Center was supposed to be translational, involving integration of clinical and basic research and required a clinical arm I was recruited to represent that. We decided the area we wanted to look at was first episodes so we designed a series of longitudinal studies.

TB: With whom did you collaborate in this study?

NS: My major collaborator was Matchei Keshavan, who continued to direct the studies after my departure. These were not traditional clinical trials. The design was longitudinal evaluation with treatment provided by the study team following an ideal approach that's been used in many other First Episode studies, in particular the Hillside Hospital study led by Jeffrey Lieberman, before he left to North Carolina. We followed a very low dose paradigm based on the work Joe McEvoy had done at the University of Pittsburgh, in which he looked for a neuroleptic threshold dose with haloperidol, based on the Haase handwriting model to detect early hypokinesia. He found, in first episode patients, the neuroleptic threshold was in the neighborhood of three to four milligrams with haloperidol, which we used in our early work. When risperidone came out in 1994, we were not able to use a neuroleptic threshold dose, because for risperidone it is much higher. So, we dosed on an empirical basis, starting at one milligram, with a target dose below four milligrams. In our early work we found the dose for risperidone was very similar to haloperidol, at about four milligrams, and that was why that dose was chosen in the Janssen trial, for which the results are unknown at this point. The model for the work we did with the first episode patients

at Pittsburgh provided clinical assessment and ongoing monitoring of patients cognitive functioning and, if feasible, included brain imaging. It was an enormously productive program because of the importance of first episode studies, particularly in patients with no exposure to antipsychotic drugs. Such studies allow us to understand manifestations present from the onset of the disease as opposed to manifestations that may be confounded with later stages and effects of treatment. Some of our findings were counter to my intuition regarding brain structural and functional abnormalities, which I believed were a function of chronicity and treatment. They turned out to be more characteristic of neurodevelopmental abnormalities that occurred earlier, since many of these were present at the onset of the disease.

TB: Did you get involved with any newer antipsychotics other than risperidone?

NS: I have had the opportunity to participate in trials and served on advisory boards for the companies developing many of these drugs. One of the drugs I was involved with was sertindole, the Lundbeck compound licensed to Abbott in the United States. At our Special Study Center at Mayview Hospital, we were also involved in a couple of studies of quetiapine, (Seroquel) with AstraZeneca, but I've not had any direct involvement with that company. I've also been involved since 1998, after I left Pittsburgh for Hillside, with Pfizer in the development of ziprasidone. Finally I've been involved in the development of aripiprazole, originally, with Otsuka the company that developed it, and then with Bristol Myers Squibb. My ties with Otsuka were closer; I was involved in the design and development of a couple of their studies. Those have been wonderful experiences. I have also served on an advisory board for Lilly regarding olanzapine, before it came to market. I have a little paperweight to prove it, which has on it Zyprex, which was the name that it was given before Zyprexa. I haven't decided whether to take that to the Antique's Road show, but maybe sometime later! I think the new antipsychotics are really exciting and I'm most interested now in long term treatment, because I think we don't know how they work until we understand how they'll do in the long term.

TB: When did you move to Hillside?

NS: In 1997 when John Kane, who I had known since residency and is now Chair of the Department at Hillside, invited me to become the Director of Research. I swallowed long and hard, but it seemed a very exciting opportunity to direct a broader program than I was working with at University of Pittsburgh. I accepted and the way I described my move is, it was from Hawaii to Hillside, because after the last ACNP meeting

here in Waikoloa in 1997 I went back to Pittsburgh, packed my bags, and moved to New York. That's where I've been since and the opportunities there have been terrific. First, one of the opportunities has been to work closely with John Kane; although we worked together before in the Treatment Strategies and Schizophrenia Study. When I arrived there were many people in the group that I had worked with and other people I had known from even earlier times, because of my collaboration with Hillside in the area of tardive dyskinesia I've worked in over the years

TB: Could you tell us about your activities at Hillside?

NS: I'm doing three things at Hillside. One is related to a project I started at the University of Pittsburgh shortly after I left NIMH. With Steve Marder at UCLA and John Kane at Hillside we compared clozapine and haloperidol and found, as we published just earlier this year, that in six months clozapine was dramatically better than haloperidol in any way we looked at the data. In a second study that we started when I was still in Pittsburgh we compared clozapine and risperidone. We completed this study after I moved to Hillside and we're in the process of analyzing those data. So that is one of the three projects I have been involved in here. In this study, of which I reported the results in a poster, we found the distinctions between risperidone and clozapine are nowhere near as sharp as those between haloperidol and clozapine. There are definitely advantages for clozapine, but also for risperidone.

TB: What about the other two projects?

NS: We have ongoing a new First Episode study in which we are comparing the effects of risperidone and olanzapine up to three years. The principal collaborators are John Kane, I, and Delbert Robinson, a newer investigator. In addition, I'm involved in another collaborative study looking at negative symptoms in schizophrenia, collaborating with Will Carpenter at the University of Maryland, Dan Javitt at NKI, and Steve Marder at UCLA. We are looking at NMDA agonists in the treatment of negative symptoms. .

TB: Your activities from the very beginning are well documented in your publications. Could you say something about your papers? What was your first paper?

NS: My first publication grew out of the first NIMH collaborative study. Its title was something like, *One Year After Discharge, Long Term Outcome*, I don't remember the rest. It was the first formal presentation I ever made at a meeting; at an annual meeting of the American Psychiatric Association. It documented the long term outcome in patients who were receiving follow-up. What was most instructive is that we found

benefits in patients who had received placebo in the short term trial. We interpreted the finding, and I still think it's the best, that patients who received placebo had slightly longer hospitalizations, during which they received extraordinary care that left them better prepared to return to the community.

TB: When and where was it published?

NS: In 1967, before I received my PhD, in the American Journal of Psychiatry.

TB: What was your most recent publication?

NS: The most recent is not a first authored publication, but I'm prepared to take major credit for it, because it was an equal collaboration. This was with John Kane and Steve Marder reporting on the clozapine and haloperidol comparison. It came out in October 2001, in the Archives of General Psychiatry.

TB: What would you consider as your most important publication?

NS: The paper I'm proudest of was the one that reported the Treatment Strategies in Schizophrenia Study, which was in the Archives, I believe, in 1997.

TB: What would you consider as your most important contribution to the field?

NS: It would be the emphasis on the study of long term treatment in schizophrenia and the importance of looking at long term treatment effects. A second one I haven't even commented on is the importance of looking at outcome measures that go beyond psychopathology. I've worked on the development of rating scales to assess social adjustment and see that as a contribution.

TB: Any other contribution you would like to mention?

NS: I think I'm a really good collaborator and mentor. It was already in my grade school report card that, "works well with others."

TB: Could you say how people responded to your findings at the time you published them?

NS: Our findings in the Treatment Strategy in Schizophrenia Study were readily recognized as a definitive statement regarding antipsychotic treatment in schizophrenia and what the limits of treatment are. On the other hand, the response to some of our findings with family treatment were extremely negative have been criticized, both in private and public, on the grounds we didn't do it right. That's OK with me, because it's my belief we did it right and the findings stand.

TB: Let me switch to something entirely different. When did you become a member of the ACNP?

NS: 1975.

TB: Would you like to say something about your ACNP activities?

NS: I was admitted in 1975, one of three women admitted that year. The other two were Magda Campbell and Jean Endicott and we doubled the number of women in the College. I have had extensive committee involvement, in two committees, in particular. I was on the Education and Training Committee, chaired that for a couple of years and it was a wonderful experience. I enjoyed meeting the young people, whom I still see at the meeting today, and felt very positive about that experience. I'm currently on the Credentials Committee. That's a very challenging experience. It is far harder to get into the ACNP today than it was in 1975, and I'm constantly dismayed at the number of people we do not admit, who might well turn out to be very positive contributors to the society. It's a tribute to the ACNP that people want to be members and I'm happy to serve in this role, but I will also be happy when I get to stop.

TB: Am I correct you are still fully active?

NS: Oh, yes.

TB: And you seem to intend to keep on going.

NS: That's absolutely correct. I see myself as busier than ever.

TB: I would like to wish you the best with your work. Thank you very much for sharing this information.

NS: It's been an absolute pleasure. Thank you very much.

GEORGE M. SIMPSON

Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 12, 1994

LH: This will be an interview with George Simpson* for the archives of the American College of Neuropsychopharmacology. We are in San Juan, Puerto Rico. It is December 12, 1994. I am Leo Hollister. What impelled you to get into medicine and psychiatry, in particular?

GS: I would have to say A. J. Cronin got me interested in medicine as a boy in Scotland, but, as I finished high school, I felt I could not go to medical school. I was not a very good student, when I reached puberty I was a bit wilder than most people. I did biochemistry at Glasgow University after I received a letter on a Friday saying I would not be called up into the Army for a year, so I went to Glasgow to the university and started on Monday. It was easier in those days to get into university. I studied biochemistry and then, when I was drafted, went to Liverpool to do "work of national importance" at Distillers, who made thirty three brands of Scotch whisky and two antibiotics; I was assigned to work with antibiotics. After completing my service obligation I went to medical school in Liverpool after seeing the Dean who was also Scottish and said, "come here and you'll be alright". I didn't apply anywhere else. So that, too, was easy. When it was over, I was dithering between pediatrics and psychiatry and finally decided to go into psychiatry. I was reading an article in the Lancet one day, while I was having tea, and there was an ad about the residency program in psychiatry from McGill by Ewen Cameron, so I wrote them a letter. They wrote a letter back accepting me, so I only applied for one residency program and went to McGill.

LH: You came to North America to do your residency?

GS: Yes, and McGill was an incredible place at that time. It was very unique because it was a department of psychiatry in 1956 that had an endocrinologist, Murray Saffrin, and Ted Sourkes who was a catecholamine person. It also had Bruce Sloan who became a Chair and it had Kral, who was a neuropsychiatrist, and Clifford Scott, who became president of the International Psychoanalytic Society. Kral felt if you couldn't see it, it didn't exist, and Clifford Scott felt that if you could say it, it wasn't important. So, that was the huge range. And, of course, Malmo, Wittkower, Shagass, Tyhurst, Boag and Cleghorn were there, as well as Lehmann. He gave us lectures, not very many, since Lehmann and

* George M. Simpson was born in Derry, Pennsylvania in 1926.

Cameron, did not get on well. Thirteen people who were there became chairs of departments. Then I decided to move to the States. I was going to spend a year in Canada, up to a year in the States and some time in Mexico and then on to London, England. I wrote letters one weekend and applied to umpteen places in the States and posted them on a Monday. Then Cleghorn spoke to me because Nate Kline had called him. I had included Rockland State Hospital in my brief application and mentioned an interest in research. The Hospital Director had given Nate Kline the letter and, as he new Cleghorn, he phoned to ask about me. I remember being less than pleased when this breezy guy from New York called and was chatting away while I was barely awake. This soon changed to pleasant thoughts when Nate told me how he had awakened a more senior Dr. Simpson, an obstetrician, and offered him a Fellowship in psychiatry. So I ended up going to New York because Nate inundated me with phone calls.

LH: Gave you the hard sell.

GS: That was how I came to Rockland.

LH: You went there on a Research Fellowship?

GS: Right. In my brief residency application I mentioned that I was interested in research. This letter was sent to all approved programs who took foreign medical graduates and paid $300/month.

LH: Were there other fellows at Rockland doing research beside you?

GS: There was the nucleus of a research group. Given there was very little research in psychiatry going on in the United States at that time, this was a somewhat eccentric group.

LH: What year would this have been?

GS: This would have been 1957.

LH: That was after Nate had done his work with reserpine and was going with Marsilid (iproniazid)?

GS: Right, so that was going on at the time. But the group was interested in Gjessing's Syndrome, doing longitudinal research. We had people doing endocrine studies looking at periodic catatonics, who were very scarce. We had a research ward and I was the doctor. I was chosen for who I was, where I came from, and my personality rather than what I knew; a typically Rockland thing. We had an investigator who appeared to believe that if you only had enough urine you could solve any problem. Every time he received grants, he bought another freezer and filled it with urine samples so that one, two or five years later, when he knew more, he could go back and analyze that urine. Then, there was the famous brown out in New York, and urine flooded the whole place.

LH: The urine bank went down the drain!

GS: That was quite funny.
LH: Was anything published from that time with your name on it?
GS: Very little was published. Nothing was happening therapeutically; we merely followed a small group of patients, some of whom were diagnosed as suffering from periodic catatonia. These patients were on continuous urine collection, thyroid measurements, etc. I put in a grant at which hypothesized baseline hormonal status would predict the therapeutic outcome to a pharmaceutical intervention. This was influenced by the work of Max Reiss and Hemphill's work in Bristol who suggested resting steroid levels predicted therapeutic outcome in insulin treatment. The grant, "Research on Endocrinology and Drugs" (RED) involved continuous monitoring of thyroid, adrenal and gonadal indices while patients were given a range of therapeutic agents for a three month period alternating with a three-month placebo period. Jonathan Cole site visited us, liked the proposal, suggested we enlarge it and ask for more money and change the PI as I was only a third year resident at the time. Nate became PI and ran it very loosely. The very independent investigators did their own thing which ultimately resulted in producing very little. I did not put my name on the final report. Retrospectively it was not a bad idea but it was the wrong patient population for drug studies. We did a lot of thyroid studies and as I became more interested in thyroid and psychopharmacology we opened a new ward for clinical trials of new agents.
LH: Those thyroid studies were mainly protein bound iodine (PBI), weren't they?
GS: Yes, and they included studies with perphenazine.
LH: Didn't you find elevations of PBI with perhenazine?
GS: We felt that some of the iodine used in the synthesis of perphenazine might have remained. We could'nt prove it; the effects were real, but small. Our other studies were a very expensive way of showing that the hospital administration changed their salt to an iodine supplement without telling us. We had previously checked the iodine intake and it was OK. In any event, all our patients had under-active thyroids, and when we went to a prison to get a control group, the prisoners all had very large thyroids. It was clear they had an iodine deficient diet which made us come back and revisit the hospital food which was now loaded with iodine. It was a very expensive lesson but taught me a lot. After that came another strange finding, that monoamine oxidase inhibitors influenced spermatogenesis.
LH: How did you find that out?
GS: One of the investigators was interested in the testes.

LH: Did he do biopsy?

GS: No, he looked at spermatogenesis and it so happened, one of the people who worked there became depressed and I treated him with a monoamine oxidase inhibitor. Then, I found out that he had been a control in the study that dealt with the testes, donating sperm samples once or twice a week for two years with low counts, motility and abnormal morphology. A few weeks after starting Nardil (phenelzine), all these indices improved dramatically. It sound improbable but I ended up with three depressed subjects, all with baseline sperm data who all showed improvement after being on Nardil for a few weeks. It was difficult to write it up and I decided a letter to the editor would be the best thing to do. So one weekend I wrote a letter which was published in JAMA. One of the authors approached me to say Nate wanted to be an author. This at the time seemed strange. Later I found out that Nate had taken out a patent on the use of MAOI's to treat infertility. Shortly after that, Newsweek or Time had a paragraph about someone in New England who had bought an expensive Argentinian bull that was performing well but producing little and they had brought in a New York psychiatrist who was giving the animal huge amounts of phenelzine. Of course, it was Nate! To complete the story, when I placed the subjects on Nardil I had stressed not to take alcohol. At that time we knew of hypertensive crises produced by alcohol in patients. I later found out all three of the subjects drank heavily; my guess is the absence of alcohol during the treatment produced the change in sperm count rather than Nardil.

LH: Are there other Nate stories?

GS: There is an unconfirmed story I tend to believe, that when they evaluated reserpine they did not find anything; you have to remember it was ward clinicians with huge patient populations who evaluated these medications. The hospital glazier said he did not know what was going on but there was diminished window brakeage in that unit. In those days the windows were glass reinforced with metal and wire.

LH: Did they give it for hypertension?

GS: No, the hypertension studies had been done before. The original Indian paper published in 1934 was on "*Rauwolfia Serpentina, a native Indian herb for the treatment of high blood pressure and insanity* . The Swiss probably thought that if it worked for hypertension maybe it would work in psychosis and the Indians were correct about both. Jack Saunders, who later came to Rockland, had been at Ciba Geigy and arranged for the reserpine studies to be moved to Rockland. When I got involved I looked at some of the Rockland data on reserpine which might be half a page in a doctor's handwriting from one patient; that was all there was

for the whole study, including demographics, outcome, side effects, etc. They didn't use rating scales at Rockland at all. I introduced rating scales to Rockland in 1960 or somewhere around there.

LH: From the way you describe your experiences at Rockland, it sounds as if you were not very close to Nate, in terms of a working relationship.

GS: By the time I got there Nate had become well known and very busy with all sorts of things. I covered his practice when he went away in the summer and, eventually, I opened a practice in the same suite of offices.

LH: A practice in New York City.

GS: Yes. We tried to do research there as well, which was interesting because one year we saw over four hundred new patients who wanted antidepressants. Few psychiatrists were using antidepressants and referrals came from strange sources. There was a man in New York who did conditioning therapy who sent patients; Albert Ellis referred patients, so they were fringe referrals. I knew Nate in work, but he was always very busy and did not socialize with any of the staff. He was a very good director when the times were good, because he was never there and never bothered with what we were doing.

LH: That's commendable, isn't it? He probably was away a good bit of time in Haiti.

GS: Right. I remember another interesting story. One of our staff was an Australian who had been in New Guinea during the war. He was a very bright chap and when Nate showed him his film about Haiti, you may remember they had no psychiatric hospitals at the time and Nate opened a new hospital with donated antipsychotics and vitamins that caused dramatic changes, he pointed out that one of the patients appeared to have beriberi. I had never seen a case of beriberi but I suspect he was right and probably all the patients were suffering from avitaminosis. Nate did a lot of traveling and took pictures. He went to Africa to visit Albert Schweitzer and also went to visit the Dalai Lama. He liked to do unusual and colorful things.

LH: He was an unforgettable character. You mentioned Jack Saunders had come from Ciba Geigy then, later on, there got to be ill feeling between him and Nate. What happened?

GS: That was related to the iproniazid study and somebody should be able tell that in more detail than I can. Clearly George Crane reported the monoamine oxidase inhibitor, iproniazid, had stimulating effects. He reported this as a side effect in patients treated for tuberculosis at Long Island, but I do not think he made the jump that Saunders and Nate did, to suggest it for the treatment of depression. What happened then was

a drug company became interested to give patients with depression iproniazid and contacted Rockland. So Saunders and another psychiatrist were involved in the study and were the senior authors. Nate also gave iproniazid to some of his private patients, and was co-author in the paper which was reported more in the lay press than scientific journals. Saunders was not a psychiatrist, he was a Southern gentleman. He was also touchy and clearly made a statement at the Academy of Sciences in New York about the discovery of iproniazid. When Nate got another Lasker Award, now for iproniazid, Saunders was incensed he had been ignored. So, he and his colleague sued, and eventually, it took ten years or more, the verdict was in his favor. Saunders left Rockland but I don't know what he did after that. My own feeling is it was a question of Nate's style and Saunders' style but clearly there was a discovery at Rockland. It was a joint discovery.

LH: When did you cut loose from Rockland?

GS: I stayed there twenty years, mainly with the ECDEU grant. That is when I first met you at Palo Alto. I applied for a grant while Jonathan Cole was still in Washington and I got it. I was now in another building and did my own thing with regard to evaluating new drugs. Everybody did their own thing in the ECDEU program.

LH: You were one of the first ECDEU units.

GS: Yes, I ran a unit.

LH: During that period, you were studying mostly antipsychotics?

GS: Right, it was a bit easier then, but we did studies with other drugs as well. For instance the most unquoted paper I ever wrote was one I presented in your presence in Birmingham in 1964, about carbamazepine before it had a name. We evaluated epileptics who were psychotic. It was not only the first study of carbamazepine in psychiatry but it also showed that in the majority of patients you could use one anticonvulsant to treat epileptic patients. We also felt that it improved mood, but that might have been the effect of increased attention.

LH: You, and Art Sugerman and Don Gallant were in the front trenches, in taking the first look at many of these drugs.

GS: Right, we often were the first to give new agents to patients and this worked well because of the practice of keeping patients in hospitals. For long periods of time with a very small number of patients we were able to show it was or was not an active antipsychotic agent. Probably Sugerman, Gallant and I looked at every antipsychotic we have today before it came on the market. Given that we knew our patients very well and saw them every day, it was not very difficult to tell whether a drug was active or not. It clearly was economical. I saw my patients every

day and by rating them once a week I could confidently state whether the drug was active and whether it produced EPS with a sample size of ten patients.

LH: You called the shot right in front of you.

GS: Yes, and most of what we know today of clozapine was reported in our first study. We reported seizures, no EPS, improvement of tardive dyskinesia and withdrawal symptoms. We also did some collaborative studies, but not as big as the VA. I remember one study where we reported seizure and abnormal liver function tests in a sample of 10 or 12 patients. There was then a double-blind study of 36 active patients which confirmed both these findings and the drug was dropped. Studies in depression were difficult to do at Rockland but we did one at Bergen Pines where we compared 300 mg vs. 150 mg doses of imipramine. It was planned as a blood level study which did not work out too well but still we showed that 300 mg was superior to 150.

LH: When you were studying carbamazepine, it was kind of unique, first, in using it as a sole anticonvulsant and, secondly, using it for a psychiatric purpose.

GS: Yes, and it was published in the proceedings of the CINP meeting in Birmingham. I submitted it to the British Journal of Psychiatry and they rejected it. They said this drug would never be used, and certainly not in Britain.

LH: In those days it had a reputation for producing aplastic anemia.

GS: Right. I never submitted the paper anywhere else, so it's still buried in that volume.

LH: You mentioned that your intention was to do a blood level study comparing low and high doses of imipramine.

GS: I brought Tom Cooper over for the laboratory. Tom did a lot of extra work, including work on lithium long before it was on the market. With lithium we got involved in the dose prediction from a single time point. Tom did the same for tricyclics.

LH: Tom Cooper has had quite a career in the measurement of drug level concentrations in the blood. Where is he now?

GS: He's still at Rockland and he spends time at the Psychiatric Institute in New York. He worked early on in the RED project and set up the PBI lab. He also did a lot of work with Ted Cranswich who was interested in thyroid. Vestergard was interested in the adrenal and Tom later did work on cortisol levels for DST. It is interesting we did dexamethasone suppression tests in the late nineteen-sixty's.

LH: It couldn't be dexamethasone that early.

GS: Vestergard, who was an endocrinologist, was doing some tests that might interfere with the pituitary adrenal axis.

LH: What led you to leave Rockland?

GS: Two things were happening. The ECDEU program was folding because there were no new drugs, particularly for schizophrenia and so I felt it was time for a change. I knew Bruce Sloan who was the Chair at USC. There had been a scandal at the local state hospital, one of these public relations things which hit the press. To repair the damage, there was a proposal to set up a modern clinical research treatment center where we would have wards for evaluations as well as labs to do measure in.

LH: Was that at Metropolitan?

GS: Right. So it seemed a good bet to go to California; it had something I was interested in and the set up looked very good. Unfortunately I was not smart enough to know the MD in charge of the state worked for Governor Jerry Brown. He was a very nice guy, but he had a falling out with Governor Brown and became a non-person. His successor was not interested in a university connection which was a mistake on his part.

LH: I see.

GS: So, one of the reasons I left Rockland was this opportunity at USC. History was running down and closing the State hospitals and it was a question of where to go to set up clinical studies. I set up a unit at Yonkers, opened a day hospital and outpatient clinic, had some scattered beds in a general hospital and an eighty bed inpatient unit at Rockland, with the notion this would all become part of a research population with acute inpatients as well as outpatients. Larry Kolb was in Albany at the time and in order to set up this program, which he agreed to, we would have to affiliate with Valhalla New York Medical College. Nate agreed to this but then, at the last minute, changed his mind. It seemed to me I was running a research unit and a routine clinical inpatient and outpatient program but now none of this was going to be part of a research center, so that pushed me to leave. I don't think Nate wanted to be reporting to the Chair at Westchester, New York Medical School.

LH: Nate never liked to be tied in with the academic people.

GS: No.

LH: In New York Henry Brill was working at Pilgrim and Hy Denber at Ward Island. Did you have any interaction with them?

GS: Yes, but I had more with Bill Turner and Sid Merlis at Central Islip; we did one or two collaborative studies. Henry Brill was always a most helpful person for research. ECDEU units like those at Central Islip and

Rockland were very independent and nobody pushed to do group or collaborative activities. ECDEU meetings were a lot of fun.

LH: One of the best hangovers in my life occurred at an ECDEU meeting.

GS: That's true and that is where I first heard you tell jokes with a Scottish accent!

LH: You were a pretty good joke teller, yourself. So, you went from New York to California to head up the Research Center at Metropolitan, but you didn't confine your California career to USC Metropolitan, did you?

GS: No, that unit folded when Farabee became the director of Mental Health for the State in place of Jerry Lackner and priorities changed. Incidentally Jerry Brown's reaction to the allegation of poorly prescribed drugs was to add an additional 30 pharmacists. Anyway, I moved back to USC full time. We did publish a paper on *Research as an Impetus to Improve Treatment*, which was data oriented. We kept people off drugs for a week except for some manics, and PCP users. We gave them diazepam at bedtime and patients with all the different diagnoses improved at one week and then resumed treatment with much lower dosages of antipsychotics than were customarily used. We did some pharmacokinetic studies in the outpatient clinic in an Asian population as well as MAO studies.

LH: This is at LA County?

GS: Yes. We did the combined monoamine oxidase inhibitor- tricylic studies, which were more safety than efficacy studies and a study of trimipramine versus placebo. We also looked at L-deprenyl as well. I think everybody welcomed that study which included the use of Parnate (tranylcypromine.). I took Parnate myself and that was one of the biggest things I did for science. I didn't drink any red wine for two weeks after taking 10 mg!

LH: The MAO inhibitors put the fear of God into you, don't they?

GS: It also gave me eighty percent inhibition about three hours after I took it and I still had about sixty percent inhibition fifteen days later.

LH: You were quite sensitive.

GS: After that, they were closing wards to save money, even though there were patients waiting for beds. So it was hard to do anything when it was like that. At about this time, Wagner Bridger invited me to go to Philadelphia.

LH: This was what date?

GS: 1983, so I came back to the Medical College of Pennsylvania to set up clinical research. There were no lectures in psychopharmacology at the medical school in 1984. It's hard to believe that when I first got there, I did one lecture on schizophrenia where I had to introduce them

to Kraepelin's diagnoses, tell them about the history and how to treat schizophrenia and about genetics. But there were three hours on the psychodynamics of schizophrenia. That was in 1984!

LH: It's hard to believe that occurred so late.

GS: Two years later, there were forty odd lectures in psychopharmacology, a research program, and a research Fellowship program. We started to do comparisons of different doses of fluphenazine, measuring blood levels as well. Despite the fact nothing was taught in psychopharmacology, many patients received thirty, forty, or fifty milligrams of Haldol (haloperidol); nobody got more than 900 mg of lithium and very few got it at all. We set up two studies immediately. In one we compared the effect of different doses of haloperidol and found that ten milligrams was as effective as twenty or thirty mg. In the lithium study we were trying to push up the upper end of the blood level. There was little data about levels of 1.5 and 1.7mEq/l, and so I tried to do a study where patients were randomly assigned to stay at a lower level or increase to a higher lithium level. It soon became obvious that we had influenced people, when the attending staff started to increase the levels of lithium because they realized that if acute manics are treated at around 0.8 to 1.0 mEq/l they will not do as well as if treated at 1.5. Also, if you cut down the amount of Haldol, patients feel better. We had started this already in California. I also went back to using Sodium Amytal (amobarbital) to treat acute mania.

LH: That was the old treatment, 500 milligrams.

GS: Yes, four times a day and that was because we saw patients where I could not decide whether their illness was getting worse or if the treatment was making them worse. So I stopped using neuroleptics to treat acute manic patients.

LH: Now, on a different topic, there's a Simpson-Angus scale for rating involuntary movements. How did you happen to get into rating scales?

GS: Part of that was that all antipsychotics we had produced Parkinsonism and in looking for newer and better drugs, I thought it might be easier to quantify the side effects than the psychopathology. That was a correct assumption. In 1964, we published a scale where we showed there was a correlation between EPS and negative symptoms. We also showed that too much EPS resulted in overall behavioral ratings going down. These were all very small sample size studies. We knew nothing about power statistics in those days. We went on and developed this scale but it had some flaws in it. I tried to use gadgetry to circumvent that but it did not help and so we went for a clinical rating where we could do comparisons of treatments and identify new agents. We included items

we thought easy to measure and also items like glabellar tap since we saw a patient who developed this sign on antipsychotics but not on placebo. We did a study to look at individual differences in EPS. We took a group of patients and increased their trifluoperazine every week until they reached a quantified amount of EPS on the scale. A rather heavy patient got 20 mg and met this minimal criterion. Another patient got 500 mg and never met criteria. We took everyone off medication and on resuming it we showed that patients needed the same doses to meet criteria from the first trial. This was also true for weight gain. We looked at relative potency of drugs. Eventually, when Scott Angus was there, we published it as a monograph. There were five papers in that monograph, all related to EPS including controlled studies of handwriting as a guide to dose and studies that showed low dosages of drugs worked as well as higher dosages.

LH: Anybody with a name like Angus must be a Scotsman, huh?

GS: Yes. Scott Angus was from Edinburgh. He went to Canada and I've kept in touch with him, but he hasn't been involved anymore in research. An anecdote I remember; I was having lunch with him and there was a group of New Jerseyites, who were drinking J & B Scotch before lunch. The barman lined up the glasses and poured. I said, "I can't understand why Americans drink J & B". Scott said, "Don't knock it. It's not bad at 9:00 o'clock in the morning." He was a good lad, a very good clinician and he wrote very well. So, I was very sorry when he left, but we had a few good years while he was with us.

LH: In recent years you've been associated with treatment and complications of treatment in schizophrenia more than with any other single topic. Is that your perception?

GS: Right. It was always an interest of mine and as fewer new drugs came along, both psychosocial treatments and side effects of antipsychotics received more attention in outpatient research. I also had an interest in lower dosages. We did studies in the 1960's, looking at sub-clinical Parkinsonism as a measure of dosing and I think that was a valid concept. We had the era of very high dosing but low doses of antipsychotics are efficacious and PET studies from the Karolinska suggest that five milligrams of Haldol gave you eighty percent occupancy, a dose that Haase suggested many years before. Then we looked at clozapine in the 1970s, and immediately recognized it was different from anything we had studied previously. We also realized that the rate limiting step in dosing any drug was EPS but the question arose how do you find the dose if the drug didn't produce EPS. After that we looked at other atypical antipsychotics, and then I participated in the Treatment

Strategies Study which was essentially a dosing study compared to a psychosocial treatment. That was an interesting study, which took about eight years. Now I have a clozapine dose response study going on. Already the doses of clozapine are creeping up so we are comparing a hundred, three hundred and six hundred milligrams of clozapine in treatment resistant patients.

LH: If you want to draw blood, I've got a lab where we can measure levels for you.

GS: Well, we're looking at blood levels and someone else has a supplemental grant looking at muscarinic receptors and cognition in that group of patients, so I feel happy still working in schizophrenia.

LH: You've had quite a career and now you're about to resume it back on the West Coast and no doubt you have many productive years ahead of you. Do you think we're going to get another grand step forward in the treatment of schizophrenia?

GS: Yes, I do. I would like to think it will come prospectively and not serendipitously, but some things will come from imaging, neuropsychiatry and genetics. But there will need to be a big step forward in terms of understanding more about the illness. If prenatal factors are involved, then prophylactic action could be helpful, such as good obstetrics. In 1939, probably for the first time in history, the people in Scotland were fed properly; because of the war and food rationing women got bigger and so did pelvises. So, good antenatal care and obstetrics will help. Birth trauma is down and nutritional status has improved. Hopefully, viral infections will be reduced and genetic research increase. I suspect we will reach a point soon that a drug like clozapine could be used early in the treatment of schizophrenia. We need earlier intervention and more specific treatments for different kinds of schizophrenia. I think the antipsychotics have improved outcome by preserving affect and permitting patients to live outside hospital.

LH: We've made a lot of people better, but not well. Well, George, I wish you a lot of luck in your venture back in California.

GS: Thank you very much.

LH: And, probably before this historical session is over, we'll be calling on you to follow up with another interview.

GS: Thank you.

EBERHARD H. UHLENHUTH

Interviewed by Jerome Levine
San Juan, Puerto Rico, December 13, 1995

JL: I'm here today on behalf of the ACNP History Task Force and it's a pleasure to be able to interview Eberhard Uhlenhuth.* I've known Uhli, as he's known to most of the psychopharmacology community, since mid 1960's when he was at Johns Hopkins University.

EU: That seems like quite a few years ago, but I became interested in psychopharmacology several years prior to our meeting. That's an interesting story in that my training at Hopkins was largely from a psychotherapeutic perspective. At that time, Hopkins was one of those places where a great deal of time was spent discussing dynamics.

JL: Was it a psychoanalytic orientation or other formulations?

EU: It was a more interpersonally oriented formulation, but it was very complex. It was largely inpatient-based training, so we had to write reports of five and six pages shortly after the patient arrived.

JL: Do you have any idea what the average length of stay was then?

EU: I don't actually know.

JL: It was at the Phipps Clinic, wasn't it?

EU: Yes and, certainly, there were patients who stayed a year or two.

JL: A far cry from managed care.

EU: We don't have anything like that any more.

JL: That's what I wanted to get across. Did you actually do residency training at Hopkins?

EU: Sure.

JL: I didn't realize that.

EU: I finished in 1956, and toward the end of that period I came under the influence of Jerome Frank, one of the leading investigators in the field of psychotherapy. He developed some of the basic methodology that has persisted in the field and have, interestingly, been transferred to psychopharmacology and so he is still, I think, very influential. For example, he developed the conceptual separation of important domains to measure in distress and dysfunction, one of his major contributions. Then he began development of a subjective self-report instrument to measure distress.

JL: The now famous SCL or Hopkins Symptom Check List?

EU: It has had a lot of names and a very large number of different people contributed to its development; but yes, it was called the Symptom

---

* Eberhard (Uhli) Uhlenhuth was born in Baltimore, Maryland in 1927.

Check List at first, then it became Hopkins Symptom Check List, and finally SCL 90, a name that has stuck.

JL: I remember the 35 version, the 58 version and the Superset, or SCL 90 version.

EU: Right. Then the instrument was transferred to psychopharmacological studies, so his work has had a tremendous impact. I was also the object of that impact, because, strangely enough, as an investigator of psychotherapy, he saw I got my first grant to do a psychopharmacological study.

JL: When was that?

EU: It was in 1958. That was the study that got me hooked up with you all because it was the one out of which came my interest in non-drug factors.

JL: By "you all", you mean the old Psychopharmacology Service Center at the National Institute of Mental Health, right?

EU: Yes.

JL: Right. When I came to the National Institute of Mental Health in 1964, that's when I met you, because you were already involved in outpatient studies.

EU: I was just thinking those initial multi-site collaborative outpatient studies started before you came, didn't they?

JL: Yes, they did. When I joined NIMH, Ron Lipman was already there and one of the early people doing the outpatient studies. I don't know if Sy Fisher and Jon Cole were the two that started it?

EU: They were. Do you remember when Sy came?

JL: No, Sy Fisher had already left by 1964, when I arrived at NIMH. It was the early 1960's, I guess, that Sy was there. The Psychopharmacology Service Center started in 1956 and Sy was one of the early people there with Jonathan Cole.

EU: I must have connected with the group in the late 1950's, or maybe 1960.

JL: What was the earliest study you did?

EU: It was a study of meprobamate, phenobarbital and placebo.

JL: So, you did controlled clinical trials, comparison studies?

EU: An early controlled clinical trial, and there were a couple of physicians seeing the patients who got very different results, which was weird.

JL: Did that take you in the direction of looking at other influences besides the pharmacological effect of the drug?

EU: Yes, although our training would have distanced us from psychopharmacology, which is really interesting. What I meant to say about that earlier was we spent this tremendous amount of time talking about the dynamics and then, at the end of the case conference, just as everybody was

leaving, somebody would say, “Oh, the patient was taking Thorazine (chlorpromazine) at such and such a dose during the same period they improved, right?”

JL: An afterthought, probably significant.

EU: For a long time psychopharmacological agents were called adjunctive agents.

JL: Was that the view at Hopkins?

EU: Absolutely. We were influenced by other institutions in the area such as Shepherd-Pratt, which was very psychoanalytically oriented. Some of our faculty were also members of their staff and also of Chestnut Lodge, where the very same thing was going on; a great focus on the psychodynamic and interpersonal factors and then, at the end, dropping in that the patient, during their improvement, happened be taking a neuroleptic.

JL: It wasn’t until 1962 that the Food and Drug Administration required proof of efficacy before a drug was marketed. Prior to that, it was only safety and I wonder if you would agree that some of the earliest clinical trials were carried out to convince our colleagues that psychopharmacologic agents were, indeed, therapeutic rather than just needing to meet a legal requirement? People in psychopharmacology were so much in the minority and the psychoanalytic and psychotherapeutic approach was so omnipresent, that incontrovertible evidence from controlled clinical trials was needed to change the view of practicing and academic psychiatrists.

EU: It raises another question; to what extent people doing psychopharmacologic studies at that time were, themselves, convinced psychopharmacological agents were very potent. People like Karl Rickels, never had any doubt about it. They plunged ahead and their studies were always positive, or, at least, their published studies were. With Karl, it was a conviction, and one that just grew out of an academic career.

JL: One that happened to be true.

EU: It turned out to be correct. He felt that so strongly he would have been inclined to be suspicious of a trial that did not indicate an agent was potent if there was already evidence for that. But there were some people who did studies in psychopharmacology that were very skeptical and I would have to say I was one of those, initially.

JL: It’s nice to know that you were open enough to prove the drugs worked. In those early days I remember drugs came onto the market before companies had to prove efficacy, then disappeared. Deanol (dimethylethanolamine) and Frenquel (azayclonol) were examples that came out briefly for unproven outpatient uses.

EU: Well, meprobamate, in retrospect, was not particularly effective. It did have an effect, but it certainly was not comparable to the benzodiazepines.

JL: On the antipsychotic side, reserpine and chlorpromazine were a somewhat similar story. Reserpine certainly had an effect, but chlorpromazine was easier to manage, and the whole phenothiazine class became the drugs of choice, just as benzodiazepines have dominated the antianxiety area.

EU: Yes, I think that's a good analogy.

JL: I remember you were particularly well versed, for a psychiatrist, in statistics and design which have played a major role in the development of psychopharmacology. Where did you get that knowledge?

EU: I had a number of abortive experiences in my training. In the earlier years I almost completed psychoanalytic training, but came into conflict with the Psychoanalytic Association in Baltimore because I needed to spend more time in my academic work. I worked for about 5 years with David Duncan of the Duncan Range Test.

JL: Was he also at Hopkins?

EU: He was in the School of Hygiene and Public Health; we struck up an association and worked very closely together for about 5 years. He thought I was going to become a statistician although that was not in my mind from the beginning so that also was aborted.

JL: He saw a good person and wanted to recruit you into the field, like we all try to get good people.

EU: Together we wrote the first multiple covariance program for a computer in FORTRAN. Now, all the packages have that. I learned a great deal from him, but it was clear to me that I was going to be a psychiatrist.

JL: That training certainly distinguished you from most of the other psychiatrists doing clinical trials at that time. The depth of your statistical knowledge, from the view at NIMH, distinguished you. Can we move on to the outpatient studies you did from the mid 1960's, and how your career has evolved?

EU: The major one was that first study with Sy Fisher and Ronnie Lipman; and I don't recall whether Mitch Balter played some role in that.

JL: What I remember and I don't know if this was a trial that you were involved in, was a study which used an active and an inactive placebo and influenced the expectations as to what the placebo response would look like. I don't know whether that was done by you?

EU: That was the second study, and I was not intimately involved. In the first study there was an experimental vs. a therapeutic set, as we called them, in which we attempted to train a therapist. That was part of our

interest in exploring interactions between pharmacological and non-specific, effects.

JL: Going back to the Jerry Frank orientation?

EU: Yes, but that turned out to be extremely complicated, so complicated we had a great deal of trouble writing it up, probably because we didn't have strong effects of either kind. It was a mistake to try to train people into attitudes that might be counter to those they held. Also, the medications that were part of the trial were not very effective, so it was an iffy business.

JL: Studying the interaction or combined effect of psychosocial treatments along with psychopharmacologic agents still isn't methodologically worked out well and it's still complex to do.

EU: Right, very complex to do.

JL: What year was it you moved from Hopkins to Chicago and what brought that about; were there changes in the type of studies you were doing?

EU: The move was in 1968 and it was one of those academic things. There was some instability in the department at Hopkins. Seymour Kety had been the Chair at Hopkins for a single year and there were interims before and after; finally Joel Elkes came and there were a lot of transitions toward the end of the period when I left. Then I was offered a position by Dan Freedman.

JL: My belief about people moving is there's both push and a pull, which causes you to make a major move and you said a little about the push but what about the pull to Chicago?

EU: Dan was very forthcoming and the terms of the move were very attractive, and so it was the usual kind of academic move.

JL: Daniel X. Freedman was a superb recruiter and knew how to pick talent. A large number of people who have been very successful in academics and other areas were mentored by him. But, you came along as a developed and known research scientist.

EU: I was somewhat established already at that point. What happened in Chicago was, over a period of years, Dan assembled an outstanding faculty and created an atmosphere in which people worked in very exciting ways. It was a marvelous time and a wonderful group of people working together. It was a harmonious department.

JL: Do you want to mention other people there at the time, so we have a little context?

EU: One of those with whom I've maintained contact is Bob Schuster, who ultimately became the Chief at NIDA and then went to another university job instead of retiring. Dan Luchins is still there. There were others, but I'm blocking on names.

JL: Let's try another way; did your research focus change? You were doing outpatient trials and looking at SAD when you moved to Chicago. Sometimes, for logistic reasons, you can't carry out the same kind of trials in a new place and I wondered what the focus of your work in Chicago was?

EU: I did continue to do clinical work and, for a period, I was interested in depression and autonomic functioning. That work did not go terribly well, because in depressed outpatients there was a lot of variability, unlike severe inpatient depression.

JL: In outpatient research you have less control over what's going on, for example whether patients are taking their medication.

EU: Also, the patients were more variable and that was one of the bigger issues. Before that, I became heavily involved with Mitchell Balter and the group that were doing surveys.

JL: Was this before you left Hopkins?

EU: It was a little before.

JL: Why don't you mention that line of research?

EU: Mitchell was starting up a set of studies in what is now called pharmacoepidemiology, although I don't think we had a name at that time.

JL: That's right. I also was involved with Mitch at that time and we had difficulty titling some of the papers we had written. We used something like the nature and character of psychotropic drug use, because we didn't have the term, pharmacoepidemiology.

EU: Right, there was no key word called pharmacoepidemiology. There was no such thing and that's interesting. Mitchell's big contribution, and how I got pulled in, was that he felt it was important to have a clinical perspective in looking at the use of psychotherapeutic agents and even street drugs. He was interested in the thesis that taking street drugs might be an effort to self medicate.

JL: Especially alcohol.

EU: I was not much involved in that. He was doing that with David Nurco in Baltimore. They were also interested in alcohol and benzodiazepines in heroin addicts.

JL: He called it the compensatory hypothesis. People were trying to compensate for the problems they were having by self-medicating.

EU: They did find white addicts appeared to be more disturbed psychologically than black addicts or the general population. They were the first to generate evidence for the thesis this might be self-medication. He went on with a large group based in the Bay area in San Francisco.

JL: Mellinger and Manheimer worked with him on that project.

EU: Right, Glen Mellinger and Dean Manheimer were the major figures there.

JL: In Washington, Ira Sisson was the collaborator.
EU: Ira Sisson, a sociologist in Washington. He was at GW, wasn't he?
JL: Yes, at GW.
EU: Mitchell was at NIMH, and I was mostly at Chicago during that time, so it was a scattered enterprise.
JL: Multidisciplinary and multi-geographical.
EU: It was his genius that he came up with the notion of doing major surveys, both in the United States and in Europe, so it became possible to look at drug use over time. It became possible to relate therapeutic drug use to clinical state and that's where a modification of the symptom checklist came in. That was probably the specific thing that got me into it; I had played some part in developing and scoring the checklist.
JL: In those days there was a lot in the press about the overuse of psychotropic drugs and there wasn't data to tell us whether it was overuse, under use or misuse, and that was the stimulus that drove Mitch to say we don't know whether we're treating too many or too few people, because there were no epidemiologic catchment area studies at that time to tell us how many people were in need of treatment or diagnosable. So, those first studies were primarily or partly aimed at knowing whether there was therapeutic under usage or over usage, because the press was saying there was over usage, but the surveys found something quite different.
EU: The opposite.
JL: Yes, and now there are public campaigns, especially in depression and anxiety, to get people to recognize when they have a psychological disorder and seek treatment.
EU: It's very interesting, because reluctance to take psychotherapeutic medications on a chronic basis continues. This is as much a current issue as it was at that time. It began around diazepam and moved to alprazolam, the hypnotics and Prozac (fluooxetine). For all of these, concern about overuse has remained in the air, first for one and then another. It's a very curious thing.
JL: And also what happens in the popular press when a medication becomes popular. It's touted as the cure of all and everything. Certainly this was the case with Prozac. It was claimed to revamp personalities and a lot of other things and, then, the pendulum starts swinging the other way and all the evils of the medicine come to the forefront. Hopefully, in most cases, the pendulum swings back to the middle and another substance is accepted in our armamentarium which, when used properly, is beneficial.

EU: There is something curious about that. It seems as though medications that are safest and effective, judged objectively, are those most liable to be critiqued. Of course, they are used a lot, just because they are effective and safe. That's the point; those are the ones most liable to get in trouble. Those we've mentioned are very safe medications and they did have very broad legitimate application. Mitchell's issue was, and I certainly share his view and remain interested, that the level of usage of a medication is not a criterion of whether it is being misused. It's the appropriateness of use that counts and to know that depends on other information; knowledge about clinical status and the therapeutic requirement of patients.

JL: That's where you played a major part in trying to find ways of doing epidemiologic studies, which would gather information without the use of actual clinicians diagnosing patients.

EU: Some indices of clinical state that would be sufficiently easy and quick to gather with other core data. These were not psychiatric epidemiological surveys, in the sense that in those surveys one had to spend the majority of time establishing the clinical condition.

JL: Those surveys were of a very large magnitude. There were thousands of interviews and they were done repeatedly. It took a lot of time, both the NIMH, and people who worked with them to design the surveys, to interact with people like you and to get the thing up and running. I'm afraid those days are, at least in the near future, over. There aren't that many people at NIMH who have the time to do this any more and funding for large scale studies is largely dried up. So it was a matter of the right people, Mitch, yourself and the other collaborators, coming together at a time when there were resources to carry out those large scale studies; they will stand for a long time as innovative and unique and it's going to be awhile before anything like that can be done again.

EU: I wonder if that's going to be true for the large clinical studies that were landmark studies.

JL: The multi-center clinical trials?

EU: The multi-center clinical trials. Outpatient and inpatient. One of the critical things, at that time, was the opportunity for scientists to come into the extramural program, not just the intramural, and not only to do their administrative work, but participate and often lead the way in large and very important studies. That is the main thing that's going to be missing. It might be some funding will be available for large studies, but the time and the kind of people who were at NIMH, I'm not so sure those will be available.

JL: That was the genius of Jonathan Cole. He recognized that to get the kind of people you need at the NIMH; you have to let them continue their scientific work, if not directly with patients and laboratories, then indirectly with colleagues.

EU: It wasn't so indirect; in planning and design the folks in the extramural programs played a very large and leading role.

JL: I meant there weren't any laboratories but that was not a big obstacle. It certainly was one of the reasons I enjoyed being at NIMH and when Jonathan Cole recruited me, it was because I could continue doing things.

EU: One of things I was amazed to find was that people I came in contact and started to work with at NIMH didn't fit the description of a bureaucrat. I was puzzled about that for quite sometime.

JL: We liked to try and give bureaucrat a good connotation, but I don't think we've quite succeeded in turning that term around.

EU: I think the connotation remains.

JL: We have to mention that, a couple of years ago, Mitch Balter, at a very young age, suddenly died.

EU: He was, I believe 69, and it was in February. I remember it quite well. He was in very good health, but those things start to happen when one gets to a certain age. .

JL: Luckily, we're both alive. Have you gone on with those studies?

EU: There is a third set of surveys that has never been fully analyzed and reported and I'm planning to work on that, at least the major parts will still be published; although the disruptions and Mitch's death certainly has slowed things down.

JL: We've covered an era in the history of psychopharmacology, psychopharmacoepidemiology and your career, starting with the earliest outpatient clinical trials of these agents and going on to pharmacoepidemiologic studies. Their utilization probably will turn out to be one very important historical segment in this evolving field of psychopharmacology. Thanks very much. It's been a very interesting interview for me.

EU: I enjoyed it too.

OLDRICH VINAR

Interviewed by Leo E. Hollister
San Juan, Puerto Rico, December 13, 1995

LH: I am Leo Hollister and the date is the thirteenth of December, 1995, and I am interviewing Oldrich Vinar* from Czechoslovakia. Oldrich, you have had so many different jobs that I have lost track of them. Can you tell us what your jobs are right now?

OV: I am a clinician but, nevertheless, my main duty is to head the Joint Laboratory of the Czechoslovak Academy of Sciences and the State Institute for Drug Control. My duty has been to choose among the compounds synthesized in the Institutes of the Academy, and identify those which might be developed for clinical use. But to tell the truth, the time I spend in the laboratory is not the largest amount of my working hours because not many compounds synthesized can be considered putative drugs. I spend most of my working time in the Prague Psychiatric Hospital where I am a consultant and I see patients. And recently I started to work in my private practice for outpatients.

LH: Well, you went being a clinician to having something to do with laboratory medicine.

OV: I have even done some work with experimental animals and on isolated organs but my main activity has always been with patients.

LH: Now, you are a Medical Doctor?

OV: Yes. I am. And also a Psychiatrist.

LH: Where did you get your training?

OV: I graduated from medical school in 1949. At that time Czechoslovakia did not have many medical doctors, because during the 2nd World War the universities were closed by the Nazis. Czechoslovakia was occupied by Germany. When I had graduated at The Charles University, I got a letter from the Ministry of Health that I had to work in a Hospital for Brain Diseases which was about seventy kilometers north of Prague, in a village, Kosmonosy. When I went there, I met the Director of the Hospital who told me there were about one thousand psychiatric patients and the only Doctor to take care of them was himself. At that time there were only forty psychiatrists left in a country with fifteen million inhabitants before the war. At that time the majority of psychiatrists in the country were Jews, and many of the others were left-wing intellectuals and communists. During the war the majority of them perished in concentration camps. So this was the reason I was sent by the

* Oldrich Vinar was born in Brno, Czechoslovakia in 1925.

Ministry of Health to the psychiatric hospital in Kosmonosy. During my studies I wished to become a neurologist, so coming to a Hospital for Brain Diseases I thought there would be neurological patients. It was a surprise to find I had to treat psychiatric patients. My first feeling was, this is terrible. What could two doctors, including one who just graduated from medical school with no experience in psychiatry, do with one thousand patients? All we could do was move through noisy wards to select the most violent and most aggressive patients for ECT. We had to care for the somatic conditions of the patients like a practitioner in remote mountains, and I also do X-rays and dentistry.

LH: Dentistry!

OV: I even had to help some patients give birth to their babies. In those years some of the female patients delivered their babies right on the wards.

LH: You were their primary care physician!

OV: Something, like that.

LH: I suppose it was your feeling that ECT at the time was so traumatic you would have liked to have a better way to treat them?

OV: I had that feeling. Fortunately, the conditions improved; new colleagues arrived, we were allowed to invite consultants and ECT could be done under general anesthesia.

LH: You no longer needed to worry about fractures of the spine and all of that. What was your first contact with psychopharmacology?

OV: For three to five years we had to treat patients with bromides and caffeine to comply with "Pavlovian medicine," forcibly introduced in Czechoslovakia in a doctrinaire, Stalinist way. According to Soviet propaganda, "protective inhibition" by sleep was the best treatment in all branches of medicine, so we used sleep therapy. It was a different from the sleep therapy in Switzerland used by Klaesi in severe psychomotor agitation. His was like a long-term "narcosis" whereas our patients were put to sleep for sixteen to eighteen hours a day. Early, we discovered we could combine bromides and barbiturates with antihistamines and that helped to keep patients asleep. So it was not a big surprise when we learned about antihistamines being effective in the treatment of schizophrenia. That was my first contact with the new drugs.

LH: With chlorpromazine?

OV: First with promethazine and then chlorpromazine. It came to Czechoslovakia in 1954, because some of our pharmacologists thought it was just a new kind of sedative and that there is no qualitative difference between the old sedatives and this new drug. By citing the results of the work of French psychiatrists, some of the Swiss psychiatrists,

and then the work of Americans we tried to persuade our authorities to import chlorpromazine and other phenothiazines. We had little success because of lack of money and ideological reasons. The trouble was that chlorpromazine and other neuroleptics or major tranquilizers, acted on the sub-cortex, and according to Pavlov the site of the mind was in the cortex, in the phylogenetically youngest and "progressive" part of the brain. Nowadays, it may sound ridiculous, but according to dialectical and historical materialism, the leading role of the working class is analogous to the leading role of the cortex in the brain. So a drug, acting on the sub-cortex could not have a decisive role in the treatment of mental diseases. We argued that the cause of the disease was in the phylogenetically old sub-cortex and we need to block this "bad boy" so the cortex could win. I became more active in these negotiations when I moved from Kosmonosy to Prague and began to work in the Department of Psychiatry of the Postgraduate Medical Institute. I could also begin to collaborate with pharmacologists at the Institute of Pharmacy and Biochemistry which belonged to the Czechoslovak Pharmaceutical Industry. They worked with Mirek Protiva who synthesized tens of putative psychotropic drugs.

LH: Were they all phenothiazines?

OV: The first ones were phenothiazines. I think it worked well for our pharmacologists and clinicians that we had to study and become familiar with, so called "higher nervous activity" and "conditioned reflexes." We were well prepared for behavioral testing of new compounds; perhaps better than in other parts of the world. When we compared the effects of promazine and chlorpromazine we realized that addition of one atom, a chlorine element to a molecule, could enhance the action of a minor tranquilizer so much it becomes a drug with robust antipsychotic effects. So, I asked Protiva whether a second chlorine atom could be added and he synthesized dichlorpromazine. To our surprise we noted dichlorpromazine had the effect of a minor tranquilizer. We got scientific evidence for that when we performed one of our first double-blind multi-center clinical trials in Europe in which the clinical effects of dichlorpromazine and chlordiazepoxide were compared.

LH: The extra chlorine decreased the effects?

OV: Yes, and it didn't work at all in psychotic patients although it had some effect in neurotic patients.

LH: I suppose reserpine did not play much of a role in psychiatry in Czechoslovakia?

OV: Quite the opposite, reserpine played an important role. For at least eight years it was believed its therapeutic action was comparable to

phenothiazines. The chairman of the psychiatry department at Charles University Medical School believed that phenothiazines would go and reserpine would stay. He argued that reserpine is an alkaloid and pharmacologists know how to study alkaloids. He said that phenothiazines induce jaundice and allergic dermatitis whereas reserpine does not cause such adverse effects. Reserpine played a significant role in my research. In the mid-1960s we could work with LSD. It was synthesized in the Institute of Pharmacy and Biochemistry in Prague. We were not dependent on the import of LSD from Switzerland. I thought the LSD-induced state was a good model for schizophrenia and we could test new drugs using that model. If a newly synthesized compound blocked the effect of LSD it should be useful in schizophrenia. Zdenek Votava, a pharmacologist, tested putative antipsychotics using the LSD model in experimental animals and I tested phenothiazines in healthy volunteers. Chlorpromazine worked best, it often blocked LSD effects. I thought if chlorpromazine, given prior to LSD, could prevent the effects it meant it would be effective as a prophylactic treatment in prevention of relapse. I tried reserpine in the model and was disappointed. Reserpine did not block and did not prevent LSD-induced symptoms. My healthy volunteers and some of the nurses in my department, participating in these experiments, were very unhappy. Some of them developed severe anxiety and depression that continued for three to four days.

LH: From what we know now, its ability to release serotonin, you might have predicted that result.

OV: Yes, now this is well understood.

LH: Did you get your chlorpromazine from Rhone Poulenc or did your own Institute synthesize it?

OV: At first, we got it from Rhone Poulenc but later we bought it from Hungary where they produced it commercially.

LH: That was a revelation from ECT to chlorpromazine, wasn't it?

OV: Yes, it was. I always keep in mind my early experience with psychiatric patients who suffered so much before chlorpromazine.

LH: It has been close to forty years since you started with chlorpromazine. Have we progressed as far as you hoped?

OV: I think that we have progressed more than I hoped.

LH: More?

OV: Yes, more that I hoped. First, I did not expect clinical experience would induce such progress in understanding the mechanism of action of psychotropic drugs, which in turn will teach us more about the activity of the human brain and lead to progress we have seen in the basic sciences. Also I did not expect we would have drugs which could prevent relapse

in a periodic disorder, like bipolar disease. And I did not expect one of the most successful ways to understand the mechanism of action of chlorpromazine would be through its side effects.

LH: For a while there was a belief you couldn't get the therapeutic effect until you got the extrapyramidal syndrome.

OV: In Europe, we have the concept of neuroleptic threshold developed by a German professor in Dűseldorf, Haase. According to his theory, you cannot have therapeutic antipsychotic effect unless the patient does not write in larger letters.

LH: Changes in handwriting.

OV: Yes. The patient tries to overcome extrapyramidal rigidity and writes larger letters.

LH: What drugs came after phenothiazine in Czechoslovakia?

OV: The first drugs after chorpromazine were not neuroleptics but antidepressants, for example, amitryptyline and nortriptyline. Then, chlorinated amitryptyline was synthesized. Commercially dosulepine or dothiepine, under the trade name Prothiaden, has been most successful.

LH: Still used widely in Britain, isn't it?

OV: The pharmaceutical company, Boots, bought the license and thanks to their marketing it is still around in many countries. One of the directions of my research was to investigate the clinical effects of new drugs. But, what has been more important for me, are the by-products of this endeavour, namely I was able to develop new clinical methods. I was lucky I could work with compounds synthesized by Protiva which were studied pharmacologically by Zdenek Votava.

LH: Now you mention Votava. Is he still alive?

OV: Unfortunately he died about five years ago.

LH: I am sorry to hear that. He used to send the most wonderful Christmas cards with his enormous family.

OV: Oh yes!

LH: He was a fine man. He was the head of the Pharmacological Institute?

OV: He was not the Director of the Institute, but Head of the group working with CNS drugs.

LH: How long did that Institute exist and when did it come into existence?

OV: This institute was founded immediately after the war. It belonged to the Czechoslovak Pharmaceutical Industry. Votava worked part time at the university and part time in the Institute for Pharmacy and Biochemistry. So he often did both basic science, and development of new drugs.

LH: I understand the war and political situation had an important influence. Czechoslovakia had first the Nazis and then the Communists, with a little brief episode of freedom. How did you weather these changes?

OV: Unfortunately its influence on my work and career was a great one. I spent about half a year of my pre-graduate studies in Paris, at Sorbonne. In 1948 I wanted to stay in Paris and finish my studies in medicine there. Since I left Czechoslovakia for France, I did not formally end my University study in Brno where I had begun. My father was angry with me for this reason and refused to send money to Paris if I did not come back and settle the formalities. So I came back. It was in February of 1948. I left my things in the dormitory of Cité Universitaire and thought I will go back in two weeks, but in that month there was the Communist coup d'état and I couldn't cross the border to return for about eleven years.

LH: So, you were a prisoner in your own country for awhile?

OV: This was the feeling I shared with the majority of Czechoslovak citizens.

LH: You mentioned you came to a meeting of the CINP in Washington in 1966, was that your first trip to the United States?

OV: Yes, I still consider it as one of the most important events in my life, and a happy one. The opportunity to leave Czechoslovakia was due to the fact, that already in 1966 some liberalization of the Communist regime could be felt. I also fulfilled one condition which facilitated the permission to go to the USA. I had a history of traveling to Congresses in the Soviet Union, Hungary, Poland and other Soviet Satellites. The authorities just counted how many times you went to the East and how many times you went to the West. So, I could manage to come to this CINP meeting in Washington. I would meet you, Nathan Kline, Heinz Lehmann, Tom Ban and other colleagues. I got several invitations to lecture in psychiatric research institutions and University Departments. I could spend about six weeks after the congress in the United States. I went to Boston on an invitation from Jonathan Cole, to Miami invited by Burton Goldstein, to Minneapolis with an invitation of Bertrum Schile. I went also to California and spent time in Palo Alto. I learned much about the activities of people involved in psychopharmacology in the United States. Do you know what helped me to travel so much? I couldn't get enough dollars exchanged. As other Czechoslovak doctors, if I wished to participate in a Congress in a Western country, I had to produce an invitation with a statement that the expenses would be covered by the organizers or with an honorarium. So I had to have the invitations before going to the United States. This was another condition to get my passport stamped, allowing me to leave Czechoslovakia. The honorariums in the invitations ranged between twenty five and one hundred dollars. The problem was that after my lecture, I was asked my

bank account number to deposit my honorarium. Of course, it was not allowed for a Czechoslovak citizen to have a bank account in dollars.

LH: No, no, no!

OV: By chance, I was lucky I could buy a US airline ticket from Delta Airlines before my trip and pay for it in Czechoslovak crowns. This entitled me to fly around the United States wherever and whenever I wished for two months. So, when I left without money I went to the nearest airport and I ate on the airplane flying across the Rocky Mountains. Often I even had to sleep on the plane.

LH: I heard of people doing this on the subway, but not on an airline!

OV: The airlines were more generous and hospitable. Sometimes the colleagues who invited me loaned me the money when it could be arranged the honorarium was deposited in their bank account.

LH: I know you have had numerous offers to come to the United States permanently, but you have stayed in Czechoslovakia. Is that because of your family?

OV: Yes, to a certain extent. But perhaps the reason was more my naiveté, optimism and hope that the political situation in Czechoslovakia would change for the better. I believed that the democratic tradition of the Masaryk's country would gradually overcome the Communist dictatorship. Even after the Soviet occupation of Czechoslovakia, when the WHO organized a seminar in Belgrade in 1969, I went back. Do you remember that meeting? We met at the seminar.

LH: I remember.

OV: It was about methods in clinical psychopharmacology. I was invited because I published, together with Zdenek Votava and Milan Horvath, probably the first book on *Methods of Psychopharmacology*. It was published by Pergamon Press in 1961. So, I came to the W.H.O. seminar. Some very important people participated, Michael Shephard from Maudsley, Jerry Levine, you, Max Hamilton and a representative of the World Health Organization who, at that time, was a Russian colleague, Boris Lebedev. Perhaps, because he had some guilty feelings about the occupation of Czechoslovakia, he and you with Donald Klein and Jerry Levine helped me get an invitation to work at NIMH in 1969. So, I spent about half a year in Washington DC at the Biometric Laboratory of the George Washington University, which cooperated with the Psychopharmacology Branch of the NIMH.

LH: What was your job in the Laboratory?

OV: The laboratory had to develop a package of methods or techniques which would facilitate the analysis of data obtained during clinical trials. This was the same task I was working on in Prague. I developed the

first version of a comparable package for Czechoslovakia in 1961. We had used it in several multicenter clinical trials organized according the model of the Veterans Administration clinical trials.

LH: Didn't you have a psychopharmacological organization in Czechoslovakia? They used to have a mid-winter meeting, as I recall.

OV: Yes. These were annual meetings. The first one took place in January 1959. The official organizers were the psychopharmacological section of the Czechoslovak Psychiatric Society, the Society for the Study of Higher Nervous Activity and the Czechoslovak Pharmacological Society. These societies were members of the Czechoslovak J.E.Purkyne Medical Society. Thanks to the different interests of the organizing societies, our meetings have been interdisciplinary. The meetings have taken place in Jeseník or Graefenberg, as the Germans call it, which is a spa and ski resort.

JH: In Jesenik?

OV: Yes. We organized the sessions in the morning beginning at eight o'clock and the afternoons were free and then we had evening meetings beginning at five o'clock until ten pm. One of the reasons for the success of the program was the train going from Prague to Jesenik went very slowly and took about six hours. Nearly all the psychiatrists interested in psychopharmacology were on this train. Just as Jonathan Cole had to travel from one institution to the other in the United States to get in contact with colleagues cooperating in a trial, I could do that on this train, so they couldn't escape. This helped me organize multcenter clinical trials in Czechoslovakia. I could say to a colleague, you promised to have at least 10 patients on drug A, B, or C and you have sent data on only seven. What is wrong? Can I expect the missing data? There was another fact which helped research but was unfortunate for routine practice. The supply of antipsychotic drugs, especially of those imported from the West, was unreliable. Often, doses had to be decreased or treatment stopped, because the drugs were not there. But, if you wished to do something more for your patients, you could be sure to have the drugs if you got involved in clinical research and agreed to follow the study design. The inclusion criteria were broad; usually a clinical diagnosis was sufficient. Only patients with contraindications, such as hepatitis or Parkinsonism were excluded. As president of the Psychopharmacology Society, I had influence over the decision which hospitals got drugs irrespective of whether they would be used for patients included in the trials. Nobody asked for any payment for participating in the multicenter clinical trials as an investigator. They were glad to come to Prague or another city for training in the use of the

rating scales. They also had their say in designing the trial, the inclusion criteria, the appropriate rating scales and the forms to be filled out.

LH: You could supervise the multi-clinical trials from Prague?

OV: I was not the only policeman. Chairmen of the University departments, senior consultants of the hospitals, and later my postgraduate students helped. Usually, they became authors of separate papers or co-authors of the final paper; its text was also discussed at the Annual Meeting in Jeseník.

LH: In recent years you have been active in pulling together a list of drugs available in other countries but not yet in the United States, and for various reasons. Do you think that we are missing out on anything that is very important or something we should have?

OV: Some of those drugs might be important for some patients. I am still surprised you get the new drugs which were synthesized in Europe after a long delay which seems not necessary. In the meantime, there are thousands of patients on those drugs in Europe and other parts of the world. I think patients in the USA could profit from those drugs. I understand I got the invitation to NIMH as somebody who knows a lot about European drugs, not only about the West European, but also the Eastern European drugs. I came in November of 1999 to NIMH with a list of drugs which I thought would be important for American psychiatric patients but which had not been available.

LH: Commercial aspects are important in the United States. Unless you can come up with a drug that would sell one hundred million dollars worth, most companies just do not have an interest.

OV: I understand that. If the FDA wishes to have the drug also tested in the United States, it is very expensive. For European companies there is a minor risk that if they do not get the drug registered by the FDA, it drug might lose credibility in Europe.

LH: For instance, sulpiride, which has been around awhile, has been offered to almost every major pharmaceutical company in the United States and nobody has picked it up. That is largely because they just didn't see enough of the market for it.

OV: The opportunity to do clinical trials is easier when the drug is approved as an investigational one. I do not know whether it helps introduce a drug to market when industry is not interested.

LH: How did Czechoslovakia deal with clozapine?

OV: At least twenty years ago we did some clozapine trials. I compared it in a double blind trial with chlorpromazine. The interest in clozapine subsided when it turned out the risk of agranulocytosis was high. Nevertheless, it remained attractive because of the lack of the extrapyramidal side

effects. European psychiatrists did not find it worked in treatment resistant patients suffering from schizophrenia. Even the advantage of the lack of extrapyramidal adverse effects, could be questioned. No statistically significant difference in their intensity or frequency was found in my double-blind trial, compared to chlorpromazine. Other clinical investigators compared clozapine to haloperidol and the difference was found. With the revival of interest in clozapine, it might help to introduce a compound synthesized in Czechoslovakia. The name of that drug is isofloxythepine. It is a tricyclic with a five atom middle ring and has antipsychotic effects with no extrapyramidal adverse effects. About five years ago, a Japanese company bought the license to develop it further, but to my knowledge, they did not work with it but developed their own original neuroleptic. So the development of isofloxythepine was delayed by these negotiations with Japan. Now we are trying to introduce it, but the synthesis is very complicated. It would be expensive to produce; especially if it is produced only for Czechoslovakia. Our pharmaceutical industry is already in private hands, so the financial aspects are much more important than before our "Velvet revolution".

LH: I see. The other atypical that is catching on in this country is Risperdal (risperidone).

OV: We, especially I, have had experience in the way risperidone has been developed. We got from Paul Janssen ritanserine, which is a specific $5HT_2$ antagonist. We worked for about two years with this compound and found that when combined with haloperidol in doses up to 3-4 milligrams, the combination did not induce extrapyramidal side effects and it has good therapeutic effects on negative symptoms. I have been recommending treating patients with this combination, increasing the dose of haloperidol in patients with predominantly positive symptoms and increasing the dose of ritanserine in patients with negative symptoms. I still think it could have a certain advantage in comparison to risperidone where the equilibrium of the $5HT_2$ antagonism and dopamine-D_2 antagonism is fixed.

LH: To mimic the dual action of the Risperdal?

OV: Yes, titrating the doses of ritanserine and haloperidol, according to the amount or intensity of negative and positive symptoms. Now, we have everything in one molecule. I wished to organize another double blind trial comparing this combination with Risperdal. Not being in charge of an inpatient department and not having found colleagues who would perform the trial, I cannot tell whether the combination is really better.

LH: That is the first time I have heard of combining ritanserine, an HT_2 antagonist, with haloperidol which is a relatively pure dopamine antagonist.

I suppose your optimism things have moved along in the last forty years is justified, especially with the prospect that clozapine may over the course of time allow better re-socialization in schizophrenics than other drugs. And, it does reduce the extrapyramidal reaction. Other than that, it has been hard to see a great deal of progress compared to what most of us hoped for forty years ago.

OV: Maybe here I can discuss some views on finding new drugs. My major concern is we find ways to treat patients with drugs we already have, with better knowledge about the differences among them. I believe there is more than a quantitative difference among antipsychotic drugs and that we still ignore differences in the individual reactivity of patients. It is more art than scientific knowledge when choosing the "right drug" for the "right patient."

LH: That's tough!

OV: I know. I learned much from you, from Sol Goldberg and other American colleagues. I spent twenty years trying to find the answer but I do not consider it a waste of time. The experience taught me we have to concentrate not only on the diagnosis, especially when the diagnosis has not been made reliably, even if operationally defined in schizophrenia. I thought symptoms well defined on a rating scale were more reliable. I used the data obtained during the operation of a continuous controlled trial. All patients admitted to the ward were treated under strict double-blind condition with signed informed consent. Assuming the affinity of an antipsychotic to a certain receptor is in relation to its therapeutic effects, I calculated the correlation coefficients between the effects of a range of six antipsychotics on symptoms defined as items on our rating scale FKP to the affinities of the drugs to different receptors; norepinephrine alpha-1, alpha-2, dopamine-D_2, and histamine-H_1, and acetylcholine receptors. I had expected the higher the affinity to a receptor whose ligand is in relation to the pathogenesis of the symptom, the better should be the therapeutic effect against this symptom. Data from more than 700 patients treated with six antipsychotics were used. From 70 coefficients, 22 were found significant with P greater than 01. At first, I was surprised, that high affinity to the dopamine-D_2 receptors correlated negatively with the therapeutic effects on incoherent thinking, disorientation, dissimulation, the neglect for appearance and in blunted affectivity. Then I realized the symptoms with high negative correlations were negative symptoms of schizophrenia. This is just one example of the use of data obtained in the course of a continuous controlled trial. One of its advantages was that we haven't had any differences between research and other patients on one ward, as all those admitted had to

be treated under double blind conditions. The other advantage of the system was that having always drug and placebo, and the drug under investigation in several colors and shapes, (provided by the Institute of Pharmacy and Bichochemistry), we could change the drugs for placebos under double blind conditions. Also the opposite was possible; the pharmacologically active compound remained the same and the color and shape of the tablet changed. Such a continuous controlled trial lasted for more than twelve to fourteen years. From that, I had data on about eight to nine hundred schizophrenic patients and about six to seven hundred depressed patients treated under double blind conditions. We published our data on each single drug tested under these conditions. I intended to do a general comparison among the effects of all drugs only when we had enough data.

LH: We couldn't do that in this country.

OV: It would have been very difficult to introduce such a system in a research institute in the USA, but what happened in 1978 to me could not happen in the US. My boss, the director of the Institute used all his political power, I was thrown out of the Institute and I had to work as a doorman in a hotel for a short time. And even worse, all our data were lost. The data was left in the Institute, and were pulped.

LH: What a pity, what a pity! Well, considering the political situation in Czechoslovakia you have done pretty well. I remember a doctor got on the wrong side of the authorities and was sent up into the mountains to a tuberculosis sanitarium.

OV: Yes.

LH: Wasn't it one of the pharmacologists, who had to treat tuberculosis patients?

OV: It was Professor Zdenek Votava, a leading Czechoslovak pharmacologist, a good friend who cooperated with me frequently. Fortunately, the sanatorium in the High Tatra Mountains was built for patients with tuberculosis in the twenties but they were mostly patients with asthma in the eighties, so Votava couldn't catch tuberculosis.

LH: You were working under some handicaps although, your universal double blind study; I would have loved to have that going!

OV: Maybe I can find a possibility to revive it in some way.

LH: What are your plans?

OV: I would like to use data from the literature, to calculate the correlation between effects of drugs on the neurotransmitter systems and their effect on symptoms defined by rating scales. What I have done, just for six neuroleptic drugs, I would like to do with more and different drugs. The FDA has such data and our Institute for Drug Control

has data which are part of the registration documentation. Having this data, I would like to correlate the ranges of drugs according to the magnitude in decrease of the scores in individual symptoms with their ranges arranged according to their affinities to the receptors of different neurotransmitters. This approach, based on the effects on symptoms, would enable me to avoid nosological diagnoses. I do not believe we will find the best drug for schizophrenia. I believe a best drug exists for the treatment of patients with a certain pattern of symptoms and another drug will be best for different pattern of symptoms. This could help also in understanding the role of different neurotransmitters in the pathogenesis of the symptoms.

LH: What you are talking about, essentially, would be a new kind of nosology where you would find the constellation of neurotransmitter's involved in the pathogenesis of the disorder in each patient and treat that, rather than what name the illness is called.

OV: That is my hope and my dream. In about twenty years we will not have nosological entities like depression or schizophrenia. Instead, we would have a dopaminergic, serotoninergic or GABAergic disorder. I know it will be much more complicated. Neverless, I do not think we are cleverer than Kraepelin or Bleuler were when trying to elaborate the nosology of mental disorders. We should use what these psychiatrists did not have; the knowledge about the therapeutic effects of drugs. We can go back from knowledge about their mechanism of action to hypotheses about the pathogenesis of the symptoms, and hopefully from patterns of symptoms to nosological entities.

LH: There is no question the DSM and the ICD classifications have clarified our concepts, but they are still old concepts that don't break new ground. What you are talking about would be a total departure.

OV: Such a new classification could be better than the old ones. There have always been discussions about what is schizophrenia. Now, we have a consensus about operational definitions. It means progress but we have to go a step farther.

LH: That will keep you busy for awhile!

OV: I am not sure I can get the data from the FDA or our Institute.

LH: Any other thoughts about your career?

OV: I never have thought about my career; I was too involved in the questions I wished to find an answer for.

LH: Has it been satisfying?

OV: I think so. I am just curious; so curious it has become my handicap. I am happy to present a paper or a poster in a Congress. And I stop there. I read something new in Science, Nature or in Neuopsychopharmacology

and, seeing new ideas, I begin to use the new knowledge in my clinical work. I was not lucky with politics and perhaps this has been good luck; I have not lost time on administrative work as director or chairman of a large department. Instead, I was able to organize work in cooperation with many colleagues in my country. Unfortunately, Czechoslovakia doesn't exist anymore. We have the Czech Republic and the Slovak one so I am afraid that to plan common projects will be more difficult. For example, we changed the name of Czechoslovak Psychopharmacological Society to the Czech and Slovak Psychopharmacological Society.

LH: You didn't split!

OV: No, we didn't split.

LH: That would be sort of ridiculous to take a small country like that and split it.

OV: It was not a good political decision to split.

LH: I wish you luck with your new classification of illnesses, because that is the way to go and we need that kind of approach. Let me think back, Prague hosted the CINP in 1972?

OV: 1970.

LH: Are you going to do it again soon?

OV: We had a regional CINP meeting last year in Prague. I am not sure whether a very large congress serves the purpose it should. It's become more of a social event.

LH: Yeah.

OV: The very big congresses could be good experiences for young colleagues to get acquainted with the great stars. For me the ACNP has been the best meeting bringing new scientific findings which can be discussed while keeping social events at the margin. Even our Czech and Slovak Annual Meetings in Jesenik are becoming too big. So, I am thinking of organizing a meeting for two to three hundred participants just to discuss how to distinguish between responders and non-responders in order to analyze trials according to this distinction. I am not sure whether we will find a sponsor for the meeting. It seems that the pharmaceutical industry is not much interested.

LH: No!

OV: We only wish to discuss the outcome criteria, who is and who is not a responder. This is what I plan to do in the next half year.

LH: You tackle seemingly simple problems that are complex, the more you go into them.

OV: I know I do.

LH: But, it is necessary to tackle them. It has been nice talking to you and I am so happy that you can travel freely now and come to these meetings. Will I see you in Melbourne?
OV: I am not sure! But, I would like to come again to the meeting of the American College.
LH: You have an honorary membership don't you?
OV: I am a foreign corresponding member.
LH: Well, OK.
OV: Thank you.

DAVID WHEATLEY

Interviewed by Leo E. Hollister
Waikoloa, Hawaii, December 12, 1997

LH: We're in Waikoloa, Hawaii for the 36th Annual Meeting of the American College of Neuropsychopharmacology. The college decided sometime ago to trace the history of psychopharmacology and the media being used are videotapes with pioneers and old timers in the field. Today, one of these pioneers and old timers is David Wheatley* from England. Welcome to Hawaii, David. You're no stranger.

DW: How welcome is to be here, after England.

LH: Obviously, your English, I always think of that wonderful saying of Shaw's that every time an Englishman opens his mouth, another one despises him, but I don't think they have to worry about your accent. Were you born in England?

DW: I was born down in the west of England in Devonshire in a place called Exeter, and that's where I was brought up before I went to Cambridge University and then to Guys Hospital in London; I stayed in London ever since.

LH: So, you graduated from Guys Hospital Medical School? Then, what did you do?

DW: I went into general practice for a number of years, but soon found it was not what I wanted to do. I was interested in research and particularly the effects of drugs. Then there was a chance meeting with Kenneth Carter. So much in life happens through chance, doesn't it?

LH: You're right.

DW: I met up with Kenneth Carter; he was working with Smith Kline and French and asked me if I could do some studies in my practice. It soon became clear I was limited by the number of patients I saw, so I conceived the idea to involve a number of other GPs in order to increase the number of patients in our studies. I set up a group of GP's from all over the country. At one time we had 500.

LH: Good grief!

DW: And we were doing clinical trials.

LH: That was the very first concept of a multi clinic study in general practice.

DW: I think it was. This was in all areas of pharmacotherapy until Kenneth Carter gave me an introduction to Jonathan Cole who suggested studies with psychotropics because it was difficult to do such studies in the States. I don't think GP's were interested. In England regulations were

* David Wheatley was born in Exeter, Devon, England in 1919. Wheatley died in 2007.

fairly lax; a doctor working on his own, particularly in general practice, could more or less do what he liked. There were no ethics committees, no need to get permission from anybody and so that was how we got started.

LH: How many years had you been in this general practice group before you switched from drugs for hypertension to psychotropic drugs?

DW: I'd been doing that about eight years. It was around 1960 I switched to psychotropics and changed the name from the General Practitioner Research Group to the Psychopharmacology Research Group. Then, I was fortunate enough to get grants from the NIMH, which continued for 12 years.

LH: So, you switched entirely to Psychopharmacology?

DW: I switched, but not entirely. I still kept some other studies going and that's useful, because you got insight into other drugs that might have psychotropic effects, like β blockers for example. I felt that it was worth keeping that connection, but my personal interest was in psychopharmacology.

LH: In a general practice setting, the kind of drugs you could study would be those for conditions in general practice. You wouldn't have done any studies with antipsychotics, but you did some antidepressants, I suppose?

DW: Yes.

LH: And a whole lot of anti-anxiety drugs?

DW: This was the main area. At that time many of the modern drugs were not available, we had barbiturates and amphetamines, and I remember doing a study with Drinamyl, a popular drug in England, known as "purple hearts.".

LH: That was dexamyl in this country.

DW: A combination of barbiturate with amphetamine, which seemed illogical. One of the first studies I did was a double blind comparison of Drinamyl, comparing it to its two components in patients with depression and with anxiety. By the way, amphetamine worked quite well.

LH: I think it's been largely underrated.

DW: I couldn't agree with you more. We could get over this problem of the lag period before the antidepressants work with amphetamines, to get an immediate effect.

LH: When you did that study of amphetamines, barbiturates and a combination, how did it turn out?

DW: As one would expect amphetamine was better to terminate depression and the barbiturate to terminate anxiety, but it was much easier to mar-

ket a blanket preparation for all forms of anxiety and depression and to hell with the diagnosis.

LH: Hanna Steinberg came up with a notion that the combination had some peculiar properties, but you didn't see that?

DW: I don't remember we did. Our methodology was pretty crude in those days.

LH: What was the first modern psychotropic drug you worked with?

DW: There was a monoamine oxidase inhibitor made by ICI which was never marketed, I don't remember the name. There were various tricyclics we studied. Trimipramine was one of the earliest. Barbiturates were on their way out and I was doing studies with the first benzodiazepines. In England, Librium (chlordiazepoxide) seemed to be the more popular; whereas, over here, Valium (diazepam,) was, but they were both available. I did some sleep studies. They were still churning out barbiturates for sleep and I remember doing one sleep study with a barbiturate we found quite useful. But we didn't have polysomnographs in those days.

LH: No polysomnographs.

DW: I worked with nearly all the new antidepressants and hypnotics as they came along, in particular the new benzodiazepine hypnotics. We go around in cycles, don't we? First, we have barbiturates and then, they're out. Then, we have the benzodiazepines, and then, they are out. Now, we have the non-benzodiazepine hypnotics and they're not without problems. I was looking at various fringe areas, like premenstrual syndrome, and assessing the effect of antidepressants on that. I remember doing studies on menopause with tricyclic antidepressants and we had quite reasonable results; everybody seemed happy with them. So, I've got to the present, when I've just completed a study in Alzheimer's with donepezil. We have a problem with that drug in England; it is too expensive.

LH: It's on the market in England?

DW: It's been on the market since April, but the government is doing its best to deter doctors from prescribing it because of the cost, saying its efficacy is not proven. It is proven and the results of our study confirmed exactly what the American study showed. It gives about an extra three years of functioning at the same level you were before deterioration, and that surely is worth having. But, there's a big battle going on in England over the cost.

LH: That's becoming an increasing issue everywhere, the high initial cost vs. the long term savings. There are these new pharmaco-economic studies.

DW: That was something we never had in the old days.

LH: No, and the techniques are somewhat questionable.

DW: One of the adverse changes I have seen is the amount of documentation necessary now in studies. Everything has to be checked and rechecked to a ridiculous extent. Why do I have to write my name twice on the same form? These days I have an assistant, who sits besides me and fills in all the headers and says, "You forgot to do this, Dr. Wheatley". She remembers to get the blood tests done and to give the patient a next appointment.

LH: She's a walking computer.

DW: That's exactly what she is, but she looks better than a computer!

LH: Am I correct that you joined John Feighner's international group?

DW: Yes, part time, in an advisory capacity. But, I still do a lot of independent work.

LH: But, on occasion, you do studies with him?

DW: Oh yes, I'm doing studies with them. Not only do they provide extra facilities, but they find the patients, too. We have Andrea Shorts over there. She's full of fun and I don't have to bother trying to find patients. They're just queuing up. They've already been screened over the telephone, so one gets very few rejects and it makes life a lot easier. It's like the old days.

LH: The old days used to be good.

DW: Why are the old days always better than the present? They always are, or seem so to people like myself.

LH: I suppose data you generate through your general practice group is perfectly okay for approval by the US. Food and Drug Administration?

DW: Oh yes.

LH: You follow the rules of the British equivalent?

DW: Exactly. We have an Association of the British Pharmaceutical Industry and they lay down guidelines for trials which are very similar to FDA requirements. Most trials in England are done to FDA standards anyway, because the US is the largest market.

LH: I used to study drugs, but these days it doesn't seem very attractive, because drug companies provide you with protocol.

DW: Yes, right.

LH: You gather the data and they take it, so you never have a chance to look at in the aggregate.

DW: I couldn't agree with you more. In the old days, I did all my own analysis.

LH: The way it's done now takes some of the fun out of doing trials.

DW: I wonder if the data should be independently analyzed, but it's a company statistician who's doing it and all you get is his results. He doesn't even provide his data sheet.

LH: Some companies in the US, after the data is analyzed, will farm it out to a professional writing firm which comes up with a final manuscript.

DW: I try to resist that. I've written everything that appears under my name.

LH: That's good.

DW: But the pressure is strong, sometimes they seek to alter the phraseology so it will fit better with results in other papers. I try and preserve the integrity of papers that have my name on them. And I still try and do some research of my own, but one is dependent these days on pharmaceutical grants. The poster I presented here was something I devised completely. When I mentioned it to a company, looking for travel funds, they very generously offered me some but said, could you put in a little bit about our drug? It wasn't that I couldn't, because it's a good drug, but that was my poster. And I have never presented a paper written by somebody else.

LH: I used to be on the road a lot, giving talks, and usually the local pharmaceutical representative would tell me his problems on the way to the lecture; my reply always was, you can't rely on me to talk about your drug. I'm not going to do it. I'm going to talk about your drug in connection with the whole field, but I'm not going to single your drug out for any special mention so the best you can hope for is some general good feeling if I make a hit, and if I don't, you're stuck.

DW: Fortunately, the two antidepressants I happened to be involved in recently both have advantages and I'm happy to talk about them.

LH: Which are they?

DW: Mirtazapine, which is useful, because most depressed patients have a sleep problem and are off their food, so they lose weight. It corrects both of those but it's not so good if you have a rather large patient, particularly if she's a lady, because she will complain bitterly of putting on weight, and it's not so good for somebody who's at work and falls asleep over her desk, which I've had happen. So you have to choose your patients carefully. But, for the majority of patients, it's good and doesn't seem to disturb sexual functioning, which is very important. With the SSRI's, I get a lot of complaints about that; people sometimes won't take them because of that. The other drug is hypericum perforatum, St. John's Wort, which has been available in Germany for the last 10 years, where it outsells Prozac (fluoxetine). When I hear a statement like that, there must be a reason, so I took part in a study done according to FDA standards. St. John's Wort did come out as good as the control drug, which was amitriptyline but there was no placebo. The beauty of hypericum is that it has no side effects so it's very easy to get depressed patients to take it. They think it's a natural

product and therefore, safe. You and I know it's not, but they don't get problems in the first few weeks while waiting for the antidepressant effect. So these are two compounds, which I'm quite happy to talk about in positive terms. I did have a problem when they launched mirtazapine in England and I got the brunt of all the publicity. The Sun, which is a rag tabloid, called and asked, "Dr. Wheatley, can you tell us about this drug that makes people sexier?" And I replied, "You certainly can't say I said that although if you're depressed and get better it may". They wanted to run a great headline, "The New Drug That Makes You Sexy".

LH: There's hardly anything better you can say to sell a drug than that!

DW: It'll be interesting to see what happens when sildenafil comes on the market from Pfizer.

LH: Unfortunately, those claims generally are overstated.

DW: Yes, they are.

LH: There's so much hype about all kinds of herbs and natural products these days that you tend to be skeptical, but if you look historically at medicine, many of our most important drugs have come from natural products.

DW: Of course, digitalis, morphine, reserpine and there are many others, too.

LH: For example tamoxifen.

DW: There seems to be a move to look more seriously at natural products and do proper studies, as we did. Another that was around when I went into practice was tincture of Valeria that supposed to be a mild tranquilizer and was used to help insomnia. I went to a meeting recently and somebody was reading a paper on tincture of Valeria reporting findings from a double blind controlled trial against placebo with sleep EEG recording showing it produced a selective increase in deep and short wave sleep compared to the placebo. That sort of study is solid evidence maybe there's something we should look at to find the active ingredient.

LH: Remember, if it's tincture, it has alcohol.

DW: It was a tincture but I think, for that study, they had put it in the form of a tablet.

LH: About 60 years ago, when I was working in a drug store, we used to have Valeria extracts. We didn't sell much, but it was available.

DW: I didn't use it much, because it didn't seem to work, but it might if it's given in the correct dose.

LH: Most of these natural products don't appeal to pharmaceutical companies, because they're not patentable. But there'll be a great rush if it

turns out St. John's Wort or Gingko Balboa works for Alzheimer's. They will find the active ingredient and synthesize something similar.

DW: One of our esteemed colleagues is a firm believer in Gingko, to the extent he's taking it himself. So I thought I'd better start taking it, but unfortunately, every preparation I've tried upsets my stomach. It gives me awful gut ache.

LH: I guess the trees grow all around, mainly in the US, at least in California. Well, you've seen these ideas come and go over the years.

DW: Hopefully, we'll be around to see some more come and go, as I'm sure they will. One of the great tragedies of research on drugs is you introduce it and it seems to pass every test, and then years after, some side effect becomes apparent, so it has to be withdrawn. I'm thinking of, I forget the generic name, but the trade name was Merital; it was an antidepressant.

LH: Nomifensine. That's an example things can unexpectedly go wrong.

DW: Exactly, but no amount of very careful testing could foresee that.

LH: They estimated that ten million people had been exposed before cases of aplastic anemia occurred. So they had no choice. They had to pull it off the market. .

DW: Yes, straight away.

LH: I imagine surveys were taken before pulling off fenfluramine. God knows how many people have taken it.

DW: I was prescribing it freely all the time and never saw any great problems, but obviously, they existed.

LH: It's a risky business.

DW: It is. And we talk about the good old days, when it was so simple.

LH: Have you ever had a drug you studied pulled?

DW: No, I've been very lucky, but it could easily have happened. I was once planning a study on thalidomide before anything was known about it but that, fortunately, fell through. That was the nearest I ever came.

LH: One of the saddest ways to develop a drug was the way they started to develop thalidomide. It was Merrell in this country that started developing thalidomide, giving practitioners five bucks a head for clinical reports on using it as a hypnotic.

DW: I think that's what we were going to do.

LH: All you had to do was fill out a form about how well the patient slept after they took it and get five bucks.

DW: For the elderly and, certainly for males, it was a very useful drug in old people's homes. It was far better than barbiturates, calming them down at night and keeping them alert during the day. But give a drug a bad name and there's no way to continue using it.

LH: Although it's coming back as a treatment for of all kinds of things, including leprosy.
DW: That's interesting.
LH: The closest thing to what you did in England, in the US was what Karl Rickels was doing before John Feighner and some others got involved.
DW: That's right. In the early days, he had a group of GP's, but they were a local group in Philadelphia and he integrated them with hospital psychiatrists, whereas my group covered every part of the nation.
LH: How do you keep track of 500 practitioners?
DW: They weren't all doing studies at the same time. I don't know how I was able to do it in the early days. There was no e-mail and no fax, simply the mail and telephone, but things went at a more leisurely pace then and we didn't have to fill in so many forms. My original form was a single sheet, which was perforated and all the doctor had to do was make marks on it for analysis. The instructions were on the back of the sheet. A lot of my earlier work was done with rather crude methods.
LH: But it worked. Sometimes I wonder if we're not overly meticulous, because despite all of the care that's taken, and trying to prevent some unexpected reaction, they still occur.
DW: They still occur so the most you can do is to take every precaution, but you're never going to be able to avoid them. You will never be able to devise an absolute fail safe method for clinical trials.
LH: When you get right down to it, as far as detecting organ toxicity, you're pretty limited clinically. We have various blood tests, liver function and urinalysis, but where do you go after that in any kind of reasonable way?
DW: Exactly. There's only one way and that's to treat and study individuals over long periods of time. Then, there is the question to whom to give a new drug? From an ethical point of view there are many cases of drug resistant depression and you have to balance the potential benefit for the patient against leaving the illness untreated.
LH: That's a constant problem, how much risk is acceptable?
DW: Exactly.
LH: There's been a lot of talk, but not a whole lot done in this country, about so called Phase IV studies; monitoring patients on already marketed drugs to pick up any odd ball complication that might not become apparent in the few hundred patients studied for the NDA. Have you ever done a Phase IV study?
DW: No. My group of GP's were more interested in shorter term studies because we have a reasonable reporting system in England; where all practitioners have a supply of what they call yellow cards for reporting

adverse effects. So they pick up quite a lot of information on long term effects that way.

LH: It's a wonderful way to gather information if you can get people to do it. You've been more successful in England with the yellow card system than, in our country, the FDA with their adverse reporting system. They put out a mailing every quarter with the forms but I don't know how many replies they get.

DW: In our country they get quite a good return so it gives you some information.

LH: The question is what they do with it. In the States they don't do a damn thing to alert the public. If they would publish, periodically, all the reports.

DW: I have a feeling it's put into a filing cabinet and maybe, ten years later, something may be done.

LH: Physicians might not make an association between a drug and side effects, but if they know there's been a similar effect before they're much more likely to do that.

DW: That's exactly right.

LH: In 1960, the AMA tried to get a reporting system and I was there to review reports of Parkinson's from antipsychotics. You'd get all this drowsiness and coordination problems in somebody taking 5 drugs. It was meaningless without more information.

DW: Yes, exactly. It needs someone with medical knowledge to coordinate such a program.

LH: I expect you've been happy with what you've been doing?

DW: I've spent a wonderful life and one of the nicest things about it is traveling, meeting colleagues like you, in various places. I remember when we met in Yugoslavia; I know you will remember that too. What I always liked about ACNP meetings in the old days was the informal discussion around the swimming pool from about 2:00 to 4:00 where I met people and talk to them. Perhaps I'd say, "I'm looking for someone to write a chapter in a book", and a colleague would reply, "I'm just the guy". Nowadays I think they've got the timing wrong, to finish at 10:30 and not start again until 2:30. It would be much better to go through to 1:00 o'clock and then have the break, with an evening session, perhaps at 7:30. Now they have two evenings for posters and a late evening session.

LH: A number of years ago some of us old timers sat down over a drink and decided we should try to organize a session the way it used to be, before we had to carry all these formal papers and slides. It was just people talking.

DW: Yes, exactly.
LH: Just people exchanging opinions about a particular subject. One other thing about the program is the increasing time spent with pure science.
DW: This is what has bothered me most at this meeting. Most of it is beyond me.
LH: That's right. We used to have topics that would be appealing to sociologists and psychologists.
DW: Now, it's dominated by basic research and this isn't even research on humans. It's mostly on rats and, admirable though the rat may be, it's not quite the same thing. I agree with you, but it happens in all societies. In our own, BAP, the British Association of Psychopharmacology, exactly the same thing has occurred.
LH: But, you haven't had a split off as we have, with the formation of the American College of Clinical Psychopharmacology.
DW: I didn't know that.
LH: Don Klein spun off a new organization called the American College of Clinical Neuropsychopharmacology.
DW: That's most interesting, because when we founded our BAP it was started by a group of clinicians, including myself, and we overlooked the basic scientists. There was outcry, of course. They said, we wouldn't have minded it if you called it the British Association for Clinical Psychopharmacology. Anyway, we realized the error and let them in, but now they dominate it.
LH: I'm not against having disciplines mixed. In fact, that's one of the big educational advantages of these organizations.
DW: You do need some input from basic science.
LH: But you need a balance.
DW: I couldn't agree more. It's losing sight of what the objective is. The objective is treating a patient.
LH: It all boils down to that and it's a very difficult task to get a balance.
DW: It's interesting to know the mechanism of action of these drugs and it's certainly important for developing new drugs, but when we are sitting with our patients, we are interested to know how to make them better. We want to know the best ways of doing that.
LH: I'm glad you found your career rewarding, as I think most of us in this organization have, and, in your case, it's going to be good for sometime to come. You're not ready to become part of history yet.
DW: I don't see myself as a historical figure.
LH: I don't know the threshold you have to pass to be that.

DW: I don't either. I'll worry about that when I find it. Meanwhile, I'll go on looking.
LH: Thank you for the interview. It's nice to see you.
DW: It was a pleasure. Thank you.

ANDREW WINOKUR

Interviewed by Andrea Tone
San Juan, Puerto Rico, December 14, 2004

AT: My name is Dr. Andrea Tone and we're at the 2004 ACNP Meeting in Puerto Rico and this morning I have the privilege of interviewing Dr. Andrew Winokur.* Thank you for joining us.

AW: Sure.

AT: Why don't we start by getting some background information on you, how you got interested in medicine? You have a BA from Yale, I see.

AW: I had a circuitous route to develop an interest in medicine. I went to Yale and was an American Studies major but had no thought about medicine. At Yale, I was involved in a volunteer organization that helps students get connected with volunteer activities. It's called Dwight Hall and it's a well-known local organization at Yale. So, I did activities like tutoring kids in the city area. One of the projects they had available was to go to the local state psychiatric hospital in Middletown, about forty-five minutes from New Haven, called the Connecticut Valley Hospital. I was paired with a patient, went each week and spent time with him. By coincidence, this was a young fellow exactly my age, nineteen when I started, who was schizophrenic. At that time the prospects for people with serious psychiatric illnesses, like schizophrenia, was very grim.

AT: This was the early 1960's?

AW: This would have been 1962 or 63. It was quickly very clear that the staff felt this fellow would be in the hospital the rest of his life; that he had no prospects for any kind of life or expectations. I got to know him well during the year, coming out each week. It was difficult to accept he had no prospect for a future life; he was my age and had no discernable physical ailments.

AT: People viewing this videotape might be interested in your description of the hospital.

AW: At that time, state psychiatric hospitals were the primary modality caring for patients with what we now call Severe and Persistent Mental Illness. There was a movement in the mid to late sixties to empty the state hospitals and care for patients in their communities, in mental health centers, but the time that I'm talking about was before that started. So the majority of severely ill psychiatric patients were still maintained in these large state hospitals, which housed thousands of patients. Subsequently, the number of patients in these facilities has

* Andrew Winokur was born in Bronxville, New York in 1944.

been very much reduced. They were large, very old buildings kind of dark, very grim. That was relatively soon after the psychopharmacological era started. Chlorpromazine, (Thorazine), was the first antipsychotic drug and the first major psychopharmacologic agent, identified in 1952, and introduced to the US a few years later, in the mid to late fifties. So, by 1962, when I had this initial experience, drugs like Thorazine were widely used but still not very well understood by the psychiatric community. It was effective in helping control acute symptoms of schizophrenia, like hallucinations or agitated behavior, but it was used in high doses and had very strong side effects, so that patients were sedated and tended to have a lot of neurological symptoms that made them walk stiffly. What this produced was a shuffling gait, so wards were filled with patients moving slowly, stiffly and often with movements of their mouths and tongues. It was definitely a grim place. I hadn't been back to the Connecticut Valley Hospital, until a year ago. I happened to give grand rounds there and it was quite an experience to go back after more than thirty years and see a lot of the same buildings. Things had changed as a result of much more effective treatment, but just the physical reminders of what it was like brought back a lot of memories.

AT: Did the patient you were paired with get attached to you?

AW: We developed, over the years, a strong bond. In fact, an unusual experience occurred at the end of the year. I was probably immature and not with great judgment, but I wanted to expand his horizons and expose him to other types of experience. The big activity in the spring at Yale is called College Week-End and I was able to arrange to have him join. We had a good time together and a good experience.

AT: That's a great thing.

AW: Still, I wondered whether, in the long run, that experience was good for him or it was bad to expose him to that striking contrast to his usual environment was, and most likely, was going to continue to be. In any event, that was a formative experience that got me thinking about psychiatry. It could have turned out the opposite way around, my feeling that going into psychiatry would be a disillusioning, grim prospect; the last thing one would want to do. Instead, it struck me as being an area where there was tremendous need and something I wanted to become involved in. Up to that point I thought psychology would be the path I might follow, so I took a couple of psychology courses, did well and enjoyed them.

AT: Your BA you said was in American Studies.

AW: That's right. Yale was at the forefront in recommending a broad liberal arts education. They still advocated the courses you needed to

be pre-med, but also wanted you to have a balanced education. The American Studies major was a perfect counterpoint to the science that I gradually started to get involved in.

AT: It's a famous program.

AW: It's outstanding and, curiously, I feel a lot of the skills and training I got in the American Studies major were among the most valuable forms of preparation for what I've been doing the last thirty years, in terms of pulling information together from a lot of disciplines. It was a very broad and integrated major. A lot of my science colleagues get paralyzed when they have to put words on paper, but writing was a big part of what we had to do, so I've enjoyed writing over the years.

AT: You decided first to pursue psychology, so how did you end up at the Tufts University School of Medicine?

AW: There were a couple of other shaping experiences. I enjoyed psychology courses and had much more affinity for them than for other science courses. I had a psychology professor who became a mentor and adviser. He talked to me about what I wanted to do. His advice was that I would have more opportunities and flexibility through a career in medicine and psychiatry. He obviously identified things I, at the time, didn't understand or appreciate. Another major formative experience happened in my junior year, when I was already committed to the pre-med track. In the midst of that year the organic chemistry and physics courses were taking a tremendous effort to get to a passable level, because these were not my natural talents. A professor in the anatomy department did something that ended up on the front page of the New York Times. His name was Jose Delgado. He dressed up in a matador's outfit and entered a bull ring with a bull that had an electrode implanted in the amygdale, an area of the brain identified with the control of aggressive behaviors. He had a short-wave transistor in hand and as the bull started to approach him he activated it, stimulating the electrode in the amygdala. The bull came to a screeching halt, turned around and timidly crept away.

AT: That's fascinating. It seems like a high risk experiment.

AW: He obviously had a lot of confidence in his research findings and clearly did this to get publicity. It was a staged event that, as I said, made the front page of the New York Times. He did this to convey the brain was the new frontier of mental health research and used it to encourage people interested in psychiatry to pursue research on the brain. I read that article, and a light bulb went on; it came together with my earlier experience at the State hospital. While I was still interested in psychology, from the day I saw that article it was clear what I wanted

to do. How to do it, how to get there, was much more of a challenge. So, I essentially went to medical school to pursue a career in psychopharmacology and biological psychiatry, but I didn't really understand what that meant or what one did to get to the point where you could do things like that.

AT: Do you remember what year that happened?

AW: That would have been 1965.

AT: So you had a clear vision, by the time you entered med school, about what you were going to do?

AW: I had a clear vision but in those years psychopharmacology was not known to a lot of people in medicine. It was a defined area, starting to come along, but people were unaware it was a career path in psychiatry one could follow.

AT: How was psychiatry taught at Tufts? Did the psychoanalytic model still prevail?

AW: The department was totally psychoanalytically oriented. Tufts is a fine medical school and I was lucky to get in, given my undergraduate background. It never even occurred to me to look for a medical school with a department of psychiatry that had more on the biological side. In my second year as a medical student, I recognized I was getting no exposure to the areas I wanted to pursue. So I made an appointment to talk to the Chairman of Psychiatry and told him about the problem I was having. He was very nice, listening and kindly nodding his head, like we tend to do in psychiatry. Finally he said, "I understand the problem and can help you". It's obvious you have a neurosis about wanting to do research on the brain; it's probably a defense mechanism, because you don't want to get too close to patients and want to kind of distance yourself in the lab". So, he offered to help by referring me to a therapist.

AT: What a great story! How did you respond?

AW: That night I'd heard about a psychopharmacology graduate program at Harvard, studying behavior in pigeons. So, I started working on a plan to take a leave of absence from medical school and apply to the graduate program where I could do research. Another key mentor helped me. I had talked to the Chairman of Pharmacology at Tufts, a cardiovascular researcher, about my frustrations. He had no advice initially; he no knowledge about a suitable program. But, a couple of days later he came running up to me, very excited, telling me that he had received a brochure about one of the first NIMH funded programs in neuroscience at the University of North Carolina. I can't remember all the people involved, but a couple of key outstanding ACNP members were involved including Morrie Lipton, a father figure to many people in

the field. Morrie had been a biochemist, had a PhD in biochemistry and went back to medical school to become a psychiatrist. Just by reading his degrees and description of interests, the program sounded like what I was looking for. Art Prange was another of the people listed in the brochure. So I called the program director and asked if I could come to visit, see what the program was about and what one had to do to get in. I had appointments with Art and with Morrie, among others in the program. I remember, vividly, when Morrie invited me into his office, and knowing nothing about why I was there, asked what he could do for me. And, I said, "Well, everybody I talked to in Boston has told me there's no such person as you so I had to come down and see for myself, find out what you are doing and how you got here". He laughed and said, "Well, you know, that's the provincial Boston outlook. There are lots of people around like me, and we can give you advice". I attended a seminar in the group that Art Prange led, where he gave an overview, this would have been 1968, of the catecholamine hypothesis of depression, based on Joe Schildkraut's article. This was the first time I had heard this kind of discussion; it was incredibly exciting and exactly on target with what I was hoping to become involved in. They said they could offer me a summer Fellowship, as a medical student, to work with them. But, they also said, that there were people right in Boston doing this kind of work and encouraged me to speak to them. Both of the individuals they mentioned had recently moved to Boston from NIMH; they were Seymour Kety and Joe Schildkraut. So I made an appointment to meet with Seymour Kety, who was wonderful. He'd just moved to Mass General but hadn't started his lab going. He recommended I speak to Joe Schildkraut at Mass Mental Health Center and, if something didn't work out, he would find something else for me. I met with Dr. Schildkraut who arranged, with a lot of effort, to find support for my working in his lab in the summer between my second and third year in medical school. I worked in Joe's lab that summer studying the effects of antidepressant drugs on the activity of brain neurotransmitters like norepinephrine that had become a focus of attention. Joe had started a project, a very important one that started a new trend looking at the effects of drugs like imipramine, given to rats in an animal model on a repeated basis for three weeks. Most of the studies, at that point, had focused on the immediate effects of antidepressants on brain chemistry in animals, although clinically, it had become well known that in patients the drugs took a longer time, administering them regularly, before an antidepressant response. The question he was interested in asking was, is there something about giving these drugs for a period of time

that causes effects to help explain how the antidepressant drugs work. I felt this was a tremendously exciting and important project to become involved in. The nature of the project meant the rats had to be injected twice a day, every day, to fit the paradigm. So, seven days a week I went in at eight in the morning and eight in the evening to inject the rats and learn how to sacrifice the animals and measure the chemicals. I couldn't wait to see the results until the next morning so I'd go in at midnight to read the results coming off the counter. I realized something was going on that was pretty profound. I just loved the work. The first project we did was an incredibly unrealistic experience for a young person starting out in research; it ended up being published in Science. It's also an example of the kind of work Joe Schildkraut allowed me to be introduced to. I loved that experience so much I ended up working any available spare time, to the extent a medical student has spare time. I took four months of elective time in the fourth year to work full time in Joe's lab. As a sign to my wife of what was coming in the future, we got married in October of my senior year on a Sunday, and Monday I was back in the lab. We delayed our honeymoon until a few months later. She's been very supportive and it was probably not unrealistic experience to find out I was focused on what was going on with the work. That was an incredible journey, going from, "where is this field and how do I get into it?" to being totally enthralled with what I was doing and the opportunity to be exposed to someone like Joe Schildkraut. He had an incredible impact on me, but I loved the research so much that I could have been persuaded to stay with research and not worry about clinical training. Joe had a talk with me and told me an important issue to think about was the difference between studying psychiatry and becoming a psychiatrist. He said I could choose what I felt was right for me, but he felt I should think seriously about the important value of becoming a psychiatrist, of developing the clinical skills, in addition to pursuing research training. That had a significant impact because, initially, I was looking for the path that would keep the research momentum going. In looking for residency programs, it helped me realize the importance of finding a place to do training that would balance the opportunity to get solid training as a psychiatrist with an opportunity to stay involved in research.

AT: It seems your medical training in psychiatry was much bifurcated; you were learning about psychoanalysis at Tufts and having this amazing experience in the lab. It must have been strange. Did the people at Tufts find out about it or warm up to it?

AW: I applied to a number of programs. Initially, only Boston programs, because my wife was from Boston and I enjoyed my relationship with Joe. I applied to the program at Tufts. They asked me to withdraw my application, based on the fact they were a small program and didn't want to give up one of their few slots to someone who wanted to go into research. At least, at that point, their orientation was different. A few years later they brought Dick Shader in to be Chairman, so in the later seventies things changed. Another person, who became a key and valued mentor, was Ross Baldessarini. I had done a clinical psychiatry rotation at Mass General and got to know Ross, at that time a young faculty member, who had come from Hopkins to Mass General. So, a lot of ACNP members have been very key mentors. Ross pleaded with me to look at programs more broadly around the country, which he felt would offer more balance between the clinical and the research opportunities than the way the programs in Boston were organized. There were some outstanding programs around the country that had developed very solid foundations and track records and trained a lot of leaders in the field. I applied to places like Yale, which has turned out so many of the leading people, and Johns Hopkins, where Ross had trained. I had a memorable interview with Sol Snyder, at the University of Chicago, which had an amazing program. I also interviewed with Herb Meltzer there. Danny Freedman was Chairman and happened to be out of town that day. I've been told that if he were in town, there's no way I would have left Chicago without having been signed on. I ended up choosing Penn as a place that seemed an incredibly good fit. They had a form of research residency program, which, if one was accepted, provided an additional year of training with an opportunity to coordinate research and clinical work throughout a more extended period of time. The director of the residency training program at Penn said to me, "We're very interested in attracting residents who have interest in research, but we're pretty rigorous about the clinical training expectations. We'll give you research training opportunities, but you're going to carry a full clinical load and we're going to be rigorous in our clinical training requirements". He thought that might not be my preferred type of opportunity but that was exactly what I was looking for, that balance. That was one of the things that sold me on Penn and the quality of the people who were there. There were a couple of residents in the program, who, while doing training in psychiatry, were also pursuing PhD's in related disciplines. I didn't realize that that was going to be applicable to me, but it impacted me. It turned out I ended up pursuing a PhD in

pharmacology while I was doing my residency training, so I followed that path of enriching my own background during residency.

AT: Why did you do that? Did you feel that the MD program, the residency, didn't give you enough theoretical moorings in pharmacology?

AW: Exactly so. Again, this research residency program did provide more flexibility. It cost a bit more time, but that was not a big deal. I was doing course work and also starting the foundation of my laboratory training experience. When I looked into it, it wasn't going to take much more to put things into the structure of a PhD program. What did appeal to me was that the pharmacology program at Penn was a very well respected, rigorous program. There was no question that, initially, some of the faculty in pharmacology had questions about the depth of my commitment. We had to rotate and give seminars. When my seminar was on some of the questions would be pretty pointed, They weren't hard-core negative but they wanted to see whether I was just looking to rip off another degree or was in this to get involved in a substantive manner, which is definitely what I was aspiring to do. The PhD program overlapped with the medical school programs so graduate students got a lot of their initial credits from the first couple of years of medical school, taking the same courses. They also gave me eight course credits from my Tufts training. They allowed me to take courses that were very relevant to a substantive background in pharmacology and related disciplines, so I did not have to repeat things I'd been exposed to and would have made it overly cumbersome. So it ended up being efficient and very rewarding as a way of balancing my training.

AT: What did you do your doctoral research on?

AW: That was another interesting and fortuitous occurrence. While I was a medical student, I did a two month elective in endocrinology at Mass General Hospital and I was fascinated by patients with endocrine disorders who seemed to have a lot of profound behavioral manifestations, typically, mood swings. I found in talking with the people in the endocrine service, that this was common. They weren't particularly interested in it but it seemed obvious that hormonal effects on emotion were an important issue. When I worked with Joe Schildkraut he allowed me to pursue a side project to my main research in that we ended up administering small doses of thyroid hormone, along with antidepressants, to the rats in his chronic model.

AT: Was it Synthroid, the substance used in people who have hypothyroid disease?

AW: Yes, exactly. We thought we were getting some interesting findings, but it was a little out of context. Then Joe came back from a meeting

very excited, having heard Art Prange give a report on the first studies in patients with depression, that adding a small amount of thyroid hormone to an antidepressant could bring about a more rapid response to treatment. This is an issue that's been discussed pro and con in the field. I went to a study group last night where Peter Whybrow, my former Chairman from Penn, was one of the presenters who talked about newer studies on exactly the same topic. This was probably 1969, and Joe had heard Art Prange present the first studies of this type. When we put together what they were reporting in patients with depression and what we believed we were seeing in the rat, looking at how small doses of thyroid hormone changed the chemical balance and response to antidepressants, it seemed to make a coherent story. So, my initial thought in looking for a dissertation project, was to follow up on this observation and try to find a way to study how thyroid hormones affect brain chemistry in a way relevant to antidepressant treatment. By good fortune, it turned out that there were quite a few developments in the field when I was starting to look for a dissertation project in 1973. The pace of advance in science was such that in 1969, just a few years earlier, a compound was identified that was the brain's regulator of the thyroid. It is called thyrotrophin releasing hormone or TRH. It was initially identified in the hypothalamus and acts on the pituitary gland to regulate the secretion of TSH, thyroid stimulating hormone, which, in turn, regulates the thyroid. The first assay to measure this hormone was developed in 1972, by Dr. Robert Utiger, who was the head of endocrinology at Penn. So, for the first time it was possible to measure this hormone, to study it and also study what regulated it. When I learned about this I made an appointment to meet with Dr. Utiger to see if I could pursue studies in his laboratory. He was very accommodating. My initial thought was we would study effects of thyroid hormone treatments on this brain regulator of the thyroid as the focus of the research. As is so often the case in science, some unexpected things happened. Dr. Utiger was an endocrinologist, to him the hypothalamus and the brain were all one and the same, an entity to provide hormones to regulate the endocrine system, the pituitary- thyroid axis. I asked him if I could employ a brain dissection technique I had learned in Dr. Schildkraut's lab to do a finer dissection of the brain, and measure TRH in different regions. Of course, that seemed to be a waste of time because we were only going to find TRH in the hypothalamus, but he was willing to allow me to do it. The very first experiment we did, I found plenty of TRH in the hypothalamus, as expected, but also found TRH in other brain regions that seemed to have nothing to do with the hypothalamus. I remember

Dr. Utiger, jokingly asking "Did you wash your hands when you did the experiment", kind of like I was contaminating the other areas. So, he made me repeat the experiment about five or six times and I kept getting the same results. He made me do a number of things to test what I was measuring in other brain regions really was TRH. Every experiment along those lines supported the idea. Art Prange had another major impact at this point. Just as we were coming to believe this compound, supposedly a hypothalamic releasing hormone, was actually present in many areas of the brain, Art and his colleagues, in 1972, had come out with a report that when they gave TRH to depressed patients, it had mood elevating, antidepressant effects. They, also, did studies in animals and found that it was not simply stimulating the thyroid. In subsequent studies where they removed the thyroid or they removed the pituitary, TRH still produced effects. So, they developed behavioral and clinical data to make this an issue of greater interest. My first experiment in the lab as I told you led to a report in Science in 1974, and now I had the finding that TRH was present, widely, throughout the brain. Dr. Utiger indulged me in the discussion to put in what seemed like wild speculation. First, because TRH was present in areas of the brain we associate with emotion and behavior, TRH might function in the manner of a neurotransmitter in the brain and second, it might be one of the messengers involved in regulating behavior. That became the start of a path that has been a lot of what I've been doing for the past thirty years or so. About half of my research time and activity has been devoted to studying TRH and TRH systems trying to understand them and how we could use the principles of what TRH is doing in the central nervous system to identify new therapeutic options for patients with psychiatric disorders. Art Prange and I, with a couple of other colleagues, last year published a paper in a journal called The Journal of Pharmacology and Experimental Therapeutics, which was a hypothesis generating article. We talked about a concept that TRH systems are important regulators or mediators of central nervous system activity and there is a potential for new drugs based on TRH and TRH analogs that might have effects on a number of neurological and psychiatric disorders. This is still a goal we are attempting to pursue and develop after these many years.

AT: What you are talking about corresponds with a grass roots understanding, at least among my friends, many of whom have hypothyroidism, myself included, with what happens if you accidentally take too much medicine. I'm not super organized with Synthroid and I don't have it lined out in little boxes so I remember exactly when I've taken it and when I haven't. There have been days when I thought, did I take it or

didn't I take it. If I take an extra pill or an extra half pill I get a burst of euphoria, lots of energy, lots of ability to concentrate and doing things twice as well. Though I don't think I suffer from depression, it's interesting how it effects one's view of the world. And I don't know if that's a placebo effect.

AW: I don't think so at all. It's the kind of observation from patients, and clinicians who listen to patients that provided a basis for thinking this is something we need to take seriously and try to understand at a more substantive level. I mentioned that the start of my interest in this area was from my experience as a medical student on the endocrine rotation. I was hearing stories from patients about relationships between changes in hormonal function and emotional states that were compelling, but the endocrinologists, because of their narrow focus, were not interested. In fact, I asked one of my attendings on the endocrine service, is this something you see a lot? His reaction was, we see it all the time and it's a big pain in the neck! It makes these people so difficult to deal with while we're trying to put them through tests to figure out if they have a pituitary tumor, or whatever the problem was. The hints have been there for years.

AT: Would this have hazards like if you were taking too much cardiac medication?

AW: Oh, absolutely, yes. The very first reports in the literature on thyroid disorders like Graves Disease and some other thyroid disorders describe a psychosomatic mind- body interrelationship in the development of thyroid problems. So, in early thyroid and Cushing's disease, in a lot of adrenocortical conditions and certainly in reproductive and menstrual cycle phenomena, there are many glimpses of important mood, behavior and hormone interrelationships where the brain comes into play. There are many people related to the ACNP, who have been major figures in this field; Ed Sachar, one of the pioneers in this field who had a great impact on my interests, Bruce McEwen who has been studying the effects of steroid hormones on brain function, Art Prange and his work on thyroid. We've had a number of members who've been leading figures in the whole area of how hormones play a role in brain function; they opened up this field. We still have a long way to go, but we have tremendous opportunities.

AT: It does seem to be a hot topic. You've done a lot of work on insomnia as well, and I wanted to ask you about that. What got you interested in it?

AW: In addition to working with Dr. Utiger and having a laboratory base, I did also want to develop background and training and skills in clinical

research. The nature of my program allowed that another fantastic ACNP member became a key mentor to me in this regard, Karl Rickels. He was my mentor for clinical psychopharmacological research. I started studying under Karl as a resident and continued to remain associated with him throughout my twenty-five years at the University of Pennsylvania. I became involved with insomnia through basic research with TRH and through a lot of clinical psychopharmacological research projects. Following Karl's interest, there was a lot of focus on clinical trials with antidepressant drugs and in anxiety. We had a chance to do some of the early work identifying problems with drugs like Valium (diazepam) in terms of people on them for a long time that had problems getting off them, who had problems with withdrawal. That was a very rich rewarding experience. One of the problems we found in people who had been on benzodiazepines for a long time, was that they would often have very pronounced problems with rebound insomnia, when we tried to take them off the drug. What made me interested in insomnia was that in our research on TRH, we became involved in studies with ground squirrels, a hibernating animal, and we found if we administered small amounts of TRH into the areas of their hippocampus, key in the regulation of hibernation, it fully woke the animal up. We did subsequent studies in ground squirrels that were not hibernating but were asleep and found that administering TRH had an activating effect. We also found that TRH in awake animals has an activity reducing effect. This lead to another paper we were fortunate enough to have published in Science, and to formulation of the hypothesis that TRH might regulate arousal, almost like a thermostat. If activity was low, it would tend to bring it up and if it was excessively high, it would tend to dampen it down. My long range goal has always been to span the basic and clinical research areas, what we call "translational research," and it seemed to me the most promising opportunity would be research in the sleep area in order to make that kind of bridge, clinically. For that, I needed to get training in sleep research, which I had not had any background in. So, I took a course at Stanford, the leading center for sleep and sleep disorders. The Director, Dr. William Dement, is a widely known expert in the field. I arranged with somebody in Philadelphia, who was an expert sleep researcher, to mentor me. So I developed a chance in mid-life to become involved in the sleep area. From that, I have had a chance to pursue research in a number of fascinating areas, partly related to insomnia. Something we've done quite a bit of is how antidepressant drugs with different pharmacologic profiles effect sleep in different ways. We did some studies with a very interesting new drug

called Modafinil or Provigil. With Modafinil we did the original studies in narcolepsy. All of this has grown from the idea sleep would be an important aspect of research to get involved in. At some point down the road we might end up doing work related to TRH and sleep. Part of our current clinical research portfolio at the University of Connecticut involves studies on different aspects of sleep in different pharmacological treatments.

AT: Why did you go to Connecticut?

AW: I went by an indirect route. I had been at Penn for twenty-five years and it was a terrific place but as you go along in your career you think about what other opportunities you might consider. I was contacted by a former colleague from Penn who was at Dartmouth. They were looking for a new director of psychopharmacology, which sounded like an appropriate title. I went to visit not expecting I could be persuaded to make a change, but the person I met I really connected with. He was the Vice-Chairman of Psychiatry at Dartmouth, named Leighton Huey. He'd come from San Diego and had some very innovative cutting edge ideas about psychiatry, where the field was going, bold changes needed to make psychiatry relevant as a discipline going into the new century. I thought he had very pertinent ideas about how psychopharmacology fit into this larger perspective. And, it felt like the right time and the right opportunity. So, I joined the department at Dartmouth in 1997, and we were having a great time working on these very innovative programs. Because of those programs the University of Connecticut invited Dr.Huey to be Chairman of Psychiatry. As soon as I heard he was moving I asked if he would be willing to have me join him. Fortunately, he was and several of us moved from Dartmouth to the University of Connecticut in 1998.

AT: I bet Dartmouth was really pleased!

AW: It was a bit of an adjustment, but we started some initiatives that were new, exciting and worthwhile. And in Dartmouth we recruited a top-flight person, Tom Mellman, to take over my role and I think they are thriving. Dartmouth has prospered and at University of Connecticut, we've got some very exciting things going. Even though I was from Connecticut and was going home, it wasn't a part of the plan. It just happened, like so many things, by coincidence and serendipity.

AT: Let me ask a few final questions and if there's anything you'd like to add, please do so. Fast forward, twenty to fifty years, what would you hope psychopharmacology has achieved and what do you think it may provide for patients and psychiatrists?

AW: We're hearing about this each day we go to the meetings. This society provides clear, accurate and indelible road maps for where we need to be going. I talked about what conditions were like when I first encountered psychiatry and the progress between my first entering the field in the mid sixties and now is striking. But in spite of the great advances and progress we made, we have a tremendous way to go beyond where we are now. Psychiatry has been evolving and understands we need a body of basic science knowledge as a foundation to build a discipline that was not present in the early years. Then it was more a belief in things without having evidence to support the ideas. We've got a tremendous way to go and this was mentioned in the President's session yesterday in which it was emphasized we need a better understanding of the fundamental mechanisms of the disorders we're dealing with to making advances in diagnoses and developing more effective and targeted treatments. As in other areas of medicine, progress is based on building on these types of foundations. So there will continue to be exciting advances in the future. Twenty to forty years from now, we'll have completely new approaches to diagnosing, not replacing our clinical knowledge and skills, but supplementing them with other approaches. Making much more substantive discreet diagnoses, and formulating treatment plans based on a much more fundamental understanding of the disorder. I continue to see this as a dynamic evolving field with immense opportunities. This is something we try to convey to the medical students at UConn. When we first came to UConn, almost no students chose to go into psychiatry. We're a small school, about eighty students, but these days we regularly have seven or eight students from each class choosing to go into psychiatry. This is because we believe passionately, and communicate to the students this is an important mission.

AT: There's been a lot of talk at this meeting about the progress neuroscience has made, yet a lot of people I've interviewed have pointed out this is a time in American society when consumer and patient confidence in pharmaceutical products, particularly, psychiatric medicines is at an all time low. There's controversy in the media about whether the FDA regulators are doing their job or are in the pockets of big pharma. Do you have any thoughts how to bring these two streams back together?

AW: That's certainly a complicated topic, so I can only take on a couple of things. In terms of delivery of healthcare, we're so constrained by regulation it's difficult to maintain the human contact and commitment you need to have to have the faith and confidence we need. I see patients with our residents and medical students in our clinic and the pace to

keep on schedule is intimidating and overwhelming. Yet, we also have financial realities. We, like all academic institutions, are facing tremendous economic hurdles, so we can't be unrealistic about that. But, I feel for our patients. I understand, to some extent, that they feel they are on an assembly line and they have problems getting medications approved by their providers. So there clearly are major impediments along those lines. We don't have perfect solutions, but I'm constantly reminding residents of our need to keep humanity in the equation and do what we can to make that connection with our patients. On the FDA side, I had the terrific opportunity to serve on their advisory committee for new psychiatric drugs from 1999 to 2003. I knew very little about the FDA or how they worked prior to that experience, and I picked up a tremendous amount of respect for the FDA and the people who worked there. They invited us to come in and participate in the training program for FDA reviewers and I was able to take advantage of that. I found a group of extremely talented and very dedicated people, who really care about what they're doing, often too much with limited resources and under tremendous pressure from multiple constituencies. From what I saw it was not for lack of diligence or goodwill on the part of the people at the FDA. Rather than blaming inefficiency or incompetence one should try to see what the expectations are vs. what the resources are and the time demands. There certainly are issues and problems that need to be confronted. But I would hate to view the FDA as a group of people who are not concerned or not working hard enough.

AT: I was very interested in some of the stuff you published with Karl Rickels.

AW: That was quite an experience working with Karl. Do you know him well?

AT: I'm trying to meet him so I can do an interview for my own purposes.

AW: He's an incredible person. I believe he may have the longest continuously funded grant from NIMH of anybody in the country.

AT: Really?

AW: I don't know for sure. The other thing is, he published a book, probably in 1968, and titled something like, *Non-Specific Effects on Treatment Outcome,* based on ideas and findings about how treatment is presented by the therapist has an effect on outcome.

AT: That's fascinating.

AW: Karl's a great guy. He's an interesting fellow.

AT: He has done so much research with the benzodiazepines and the withdrawal problems

AW: We had this single case on a very standard dose of fifteen milligrams of diazepam a day, where we were able to, absolutely and irrevocably, demonstrate a profound withdrawal reaction. If you read the details of

what we saw and described and read a textbook description of the serious withdrawal reaction from benzos, it's right there in that one case. At that time, people did not believe standard doses could be associated with a withdrawal reaction. Before that time, it was only huge doses or combined with a lot of other medications people reported on with withdrawal reactions.

AT: The big emphasis was on people who take twenty or thirty pills a day, rather than a low dose.

AW: Exactly. Karl was very willing, at the front of the pack, to recognize this was an issue, and talk about in spite of the fact he gets tremendous funding from industry. Yet he would go to a company from whom he was getting a lot of funding and say, "We're seeing a lot of problems with your drug". They'd say, "Thank you, we really need to know something like this." He developed a major program to study problems of discontinuation from benzodiazepines.

AT: Right and he has a formula for tapering them off.

AW: He laid the groundwork, so we know how to do it safely. Rather than only seeing one side of the picture, he was open to the benefits and limitations. Karl still believes the benzos can be beneficial if used properly. And, I agree with that one hundred percent.

AT: Do you think they're better as a front line treatment for anxiety or is it best to mix them with an SSRI?

AW: We're clearly using the SSRIs more as the major modality. And because benzos are picking up such a negative rap a lot of my colleagues are extremely leery of using them.

AT: Stephen Stahl said you can divide the profession into those who won't touch them, and those who say okay, but with caution.

AW: Used with caution, they're very valuable and important resources. That's why we need the evidence base to understand the parameters we're working on.

AT: What do you think of Xanax XR?

AW: I had a lot of reservations about Xanax (alprazolam.) I felt the withdrawal problems were much more of an issue than with other benzos. I've used it a little, not a huge amount, of Xanax XR and we've had less of a problem.

AT: Is there anything you wanted to add?

AW: You've covered most of the things worth chatting about.

AT: Thanks for joining us.

AW: My pleasure.

INDEX

Note: The page numbers for each interviewee's entry appear in boldface type

The College

The American College of Neuropsychopharmacology (ACNP), founded in 1961, is a professional organization of leading scientists. The core purpose of the College is to contribute to alleviating human suffering by advancing the dissemination of knowledge related to the biology of the brain as well as the biology, prevention, and treatment of brain disorders; by promoting emergence of pioneering young scientists as leaders within our College and within their fields of science; and by facilitating the collaboration among relevant organizations and agencies.

The Series

The 10 volumes in this series record a fifty year history of neuropsychopharmacology related by 213 pioneer clinical, academic, industrial and basic scientists in videotaped interviews, conducted by 66 colleagues between 1994 and 2008. These volumes include a preface by the series editor placing its contents in an historical context and linking each volume to the next. Each volume is dedicated to a former President of the ACNP and edited by a distinguished historian or Fellow of the College who provides an introduction to its themes and a biography of each scientist's career. The series provides insights into a half century of discovery and innovation with its rewards and disappointments, progress and setbacks, including future expectations and hopes for the field as a whole and the ACNP as an organization.

In This Volume

In the first three volumes of this series interviewees reflect on their contributions to studying the effect of psychotropic drugs on behavioral parameters (Volume One – Starting Up), and on electrical activity (Volume Two – Neurophysiology) and molecular structures in the brain (Volume Three – Neuropharmacology). In this Volume (Volume Four: Psychopharmacology) the emphasis shifts and interviewees talk about their contributions to studying the clinical effects of psychotropic drugs. The transcripts of Volume Four give an account on the development of the new methodology used in the clinical evaluation of these drugs, as well as how the new methodology helped pharmacotherapy to become the primary form of treatment in psychiatry. Dedicated to the memory of Arnold J. Friedhoff, President ACNP, 1978, Volume 4 is edited by Jerome Levine, one of the architects of the methodology employed in efficacy studies with psychotropic drugs.